SEARCH REQUEST FORM

Scientific and Technical Information Center

Requester's Full Name: Jeffrey E. Russel Examiner #: 62785 Date: 12-2-2004

Art Unit: 1654 Phone Number 571-272-0969 Serial Number: 10/696,268

Mail Box and Bldg/Room Location: REM 3C18 (mailbox), 3D19 (office) Results Format Preferred (circle): PAPER DISK E-MAIL

If more than one search is submitted, please prioritize searches in order of need.

****

Please provide a detailed statement of the search topic, and describe as specifically as possible the subject matter to be searched. Include the elected species or structures, keywords, synonyms, acronyms, and registry numbers, and combine with the concept or utility of the invention. Define any terms that may have a special meaning. Give examples or relevant citations, authors, etc, if known. Please attach a copy of the cover sheet, pertinent claims, and abstract.

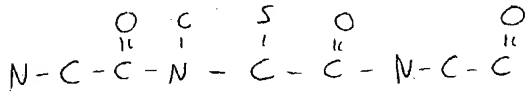
Title of Invention: Use of 3-position Cyclosporin Derivatives For Hair Growth

Inventors (please provide full names): S. Kim, Y. Yoon, M. Kim, J. King, H. Kim, H. Lee

Earliest Priority Filing Date: 6-2003

For Sequence Searches Only Please include all pertinent information (parent, child, divisional, or issued patent numbers) along with the appropriate serial number.

Please search the following partial structure:



If there are many hits, please use the keywords cyclosporin?, ciclosporin? to narrow them down.

Thank you.

JER

****

STAFF USE ONLY

Searcher: _____

Searcher Phone #: _____

Searcher Location: _____

Date Searcher Picked Up: _____

Date Completed: _____

Searcher Prep Review Time: _____

Clerical Prep Time: _____

Online Time: _____

Type of Search

NA Sequence (#)_____

AA Sequence (#)_____

Structure (#) _____

Bibliographic _____

Litigation _____

Fulltext _____

Patent Family _____

Other _____

Vendors and cost where applicable

STN _____

Dialog _____

Questel/Orbit _____

Dr.Link _____

Lexis/Nexis _____

Sequence Systems _____

WWW/Internet _____

Other (specify) _____

PTO-1590 (8-01)

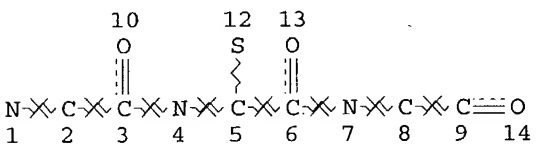
```
=> file hcaplus
FILE 'HCAPLUS' ENTERED AT 14:15:44 ON 03 DEC 2004
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
COPYRIGHT (C) 2004 AMERICAN CHEMICAL SOCIETY (ACS)
```



```
FILE COVERS 1907 - 3 Dec 2004  VOL 141 ISS 23
FILE LAST UPDATED: 1 Dec 2004  (20041201/ED)

 This file contains CAS Registry Numbers for easy and accurate
 substance identification.

=> d stat que
L4                STR
```




```
NODE ATTRIBUTES:
NSPEC    IS RC      AT    1
NSPEC    IS RC      AT    2
NSPEC    IS RC      AT    3
NSPEC    IS RC      AT    4
NSPEC    IS RC      AT    5
NSPEC    IS RC      AT    6
NSPEC    IS RC      AT    7
NSPEC    IS RC      AT    8
NSPEC    IS RC      AT    9
NSPEC    IS RC      AT   12
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS  13

STEREO ATTRIBUTES: NONE
L6           296 SEA FILE=REGISTRY SSS FUL L4
L7            65 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L6
L8            21 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L7 AND (CYCLOSPORIN? OR
                 CICLOSPRIN?)


=> d ibib abs hitrn 18 tot

L8   ANSWER 1 OF 21  HCAPLUS  COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER:         2004:582371  HCAPLUS
DOCUMENT NUMBER:          141:307037
```

TITLE: Branches on the α-C atom of **cyclosporin** A residue 3 result in direct calcineurin inhibition and rapid cyclophilin 18 binding

AUTHOR(S): Zhang, Yixin; Baumgrass, Ria; Schutkowski, Mike; Fischer, Gunter

CORPORATE SOURCE: Max Planck Research Unit for Enzymology of Protein Folding, Halle/Saale, 06120, Germany

SOURCE: ChemBioChem (2004), 5(7), 1006-1009
CODEN: CBCHFX; ISSN: 1439-4227

PUBLISHER: Wiley-VCH Verlag GmbH & Co. KGaA

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The immunosuppressive drug **cyclosporin** A (CsA) is a bifunctional mol. It directly inhibits the peptidylprolyl cis/trans isomerase (EC number 5.2.1.8) (PPIase) cyclophilin 18 (Cyp18), while the resulting Cyp18-CsA binary complex targets the serine/threonine phosphatase (EC number 3.1.3.3) calcineurin (CaN) through a gain-of-function mechanism. Whereas CaN inhibition is thought to be the main contribution of CsA in immunosuppression, many recent findings have also indicated essential roles of Cyp18 in various cellular events. For example, Cyp18 is required for the HIV-1 life cycle. To dissect the numerous biol. effects involved in CsA treatment and distinguish the Cyp18 and CaN inhibition, the design of CsA derivs. that inhibit CaN specifically would shed new light in this field. Several CsA derivs. were studied for the inhibition of Cyp 18 PPIase CaN phosphatase activity. The results indicate that Sar3 substitutions can influence CsA structure and result in direct CaN inhibition.

IT **108466-62-2 151436-10-1**
RL: PAC (Pharmacological activity); BIOL (Biological study)
(branches on the α-C atom of **cyclosporin** A residue 3 result in direct calcineurin inhibition and rapid cyclophilin 18 binding)

REFERENCE COUNT: 28 THERE ARE 28 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 2 OF 21 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2004:372845 HCAPLUS
DOCUMENT NUMBER: 140:380253

TITLE: Use of 3-position **cyclosporin** derivatives for hair growth

INVENTOR(S): Kim, Sang-Nyun; Yoon, Yeo-Kyeong; Kim, Moon-Moo; Kim, Jong-Il; Kim, Seung-Jin; Kim, Hyung-Jin; Lee, Heon-Sik

PATENT ASSIGNEE(S): S. Korea

SOURCE: U.S. Pat. Appl. Publ., 28 pp., Cont.-in-part of U.S. Ser. No. 141,723.
CODEN: USXXCO

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 2

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2004087496	A1	20040506	US 2003-696268	20031029
US 2003186857	A1	20031002	US 2002-141723	20020509
US 6790830	B2	20040914		
US 2003207798	A1	20031106	US 2002-303281	20021125
US 6762164	B2	20040713		
WO 2004041221	A1	20040521	WO 2003-KR2305	20031030

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM,

PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ
RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2002-141723 A2 20020509
KR 2002-67751 A 20021104
KR 2001-25682 A 20010511

OTHER SOURCE(S): MARPAT 140:380253

AB The invention discloses a hair growth promoting agent comprising a **cyclosporin** derivative as an active ingredient, and more particularly, a hair growth promoting agent comprising a **cyclosporin** A derivative in which sarcosine is substituted with thiosarcosine in the 3-position as an active ingredient. Preparation of e.g. [D-2-ethylthio-Sar3] **cyclosporin** A is described.

IT **683774-68-7P 683774-69-8P 683774-70-1P 683774-71-2P 683774-72-3P 683774-73-4P 683774-74-5P**
RL: COS (Cosmetic use); PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(**cyclosporin** derivs. for hair growth)

IT **683774-61-0 683774-62-1 683774-63-2 683774-64-3 683774-65-4 683774-66-5 683774-67-6**
RL: COS (Cosmetic use); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**cyclosporin** derivs. for hair growth)

L8 ANSWER 3 OF 21 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2004:131208 HCAPLUS
DOCUMENT NUMBER: 140:304074
TITLE: Semisynthetic di- and tri-functionalized non-immunosuppressive **cyclosporin** A derivatives as potential anti-HIV 1 drugs
AUTHOR(S): Carry, Jean-Christophe; Evers, Michel; Barriere, Jean-Claude; Bashiardes, Georges; Bensoussan, Claude; Gueguen, Jean-Christophe; Dereu, Norbert; Filoche, Bruno; Sable, Serge; Vuilhorgne, Marc; Mignani, Serge
CORPORATE SOURCE: Centre de Recherche de Paris, Aventis Pharma S.A., Vitry-sur-Seine, 94403, Fr.
SOURCE: Synlett (2004), (2), 316-320
CODEN: SYNLES; ISSN: 0936-5214
PUBLISHER: Georg Thieme Verlag
DOCUMENT TYPE: Journal
LANGUAGE: English

AB A regio- and stereoselective synthesis of original semisynthetic di- and tri-functionalized non-immunosuppressive **cyclosporins** starts from **cyclosporin** A (CsA) and [4'-hydroxy-MeLeu]4-CsA by way of a Barton ester decarboxylation and a C-thioalkylation. The CsA derivs., having -SMe replaced for -CH:CHMe at residue 1 and introduction of -SCH2CH2NEt2 at sarcosine residue 3, show anti-HIV activity.

IT **215531-94-5P 676618-76-1P**
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(semisynthetic di- and tri-functionalized non-immunosuppressive **cyclosporin** A derivs. as potential anti-HIV 1 drugs)

REFERENCE COUNT: 33 THERE ARE 33 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 4 OF 21 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2004:47768 HCAPLUS
DOCUMENT NUMBER: 140:263758
TITLE: Substitution in Position 3 of **Cyclosporin** A Abolishes the Cyclophilin-mediated Gain-of-function Mechanism but Not Immunosuppression
AUTHOR(S): Baumgrass, Ria; Zhang, Yixin; Erdmann, Frank; Thiel, Andreas; Weiwad, Matthias; Radbruch, Andreas; Fischer, Gunter
CORPORATE SOURCE: Max Planck Research Unit for Enzymology of Protein Folding, Halle-Saale, D-06120, Germany
SOURCE: Journal of Biological Chemistry (2004), 279(4), 2470-2479
CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Binary complex formation between the immunosuppressive drug **cyclosporin** A (CsA) and cyclophilin 18 is the prerequisite for the ability of CsA to inhibit the protein phosphatase activity of calcineurin, a central mediator of antigen-receptor signaling. We show here that several CsA derivs. substituted in position 3 can inhibit calcineurin without prior formation of a complex with cyclophilin 18. [Methylsarcosine3]CsA was shown to inhibit calcineurin, either in its free form with an IC50 value of 10 μM, or in its complex form with cyclophilin 18 with an IC50 of 500 nM. [Dimethylaminoethylthiosarcosine3] CsA ([Dat-Sar3]CsA) was found to inhibit calcineurin on its own, with an IC50 value of 1.0 μM, but was not able to inhibit calcineurin after forming the [Dat-Sar3]CsA-cyclophilin 18 binary complex. Despite their different inhibitory properties, both CsA and [Dat-Sar3]CsA suppressed T cell proliferation and cytokine production mainly through blocking NFAT activation and interleukin-2 gene expression. Furthermore, to demonstrate that [Dat-Sar3]CsA can inhibit calcineurin in a cyclophilin-independent manner in vivo, we tested its effect in a Saccharomyces cerevisiae strain (Δ12), in which all the 12 cyclophilins and FKBPs were deleted. [Dat-Sar3]CsA, but not CsA, bypassed the requirement for cellular cyclophilins and caused growth inhibition in the salt-stressed Δ12 strain.

IT **108466-62-2 210760-77-3 674802-84-7**
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(substitution in position 3 of **cyclosporin** A abolishes the cyclophilin-mediated gain-of-function mechanism but not immunosuppression)

REFERENCE COUNT: 50 THERE ARE 50 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 5 OF 21 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2003:928882 HCAPLUS
DOCUMENT NUMBER: 140:146494
TITLE: Synthesis of non-immunosuppressive cyclophilin-Binding **cyclosporin** A derivatives as potential anti-HIV-1 drugs
AUTHOR(S): Evers, Michel; Barriere, Jean-Claude; Bashiardes, Georges; Bousseau, Anne; Carry, Jean-Christophe; Dereu, Norbert; Filoche, Bruno; Henin, Yvette; Sable, Serge; Vuilhorgne, Marc; Mignani, Serge
CORPORATE SOURCE: Aventis Pharma S.A., Centre de Recherche de Paris, Vitry-sur-Seine, 94403, Fr.
SOURCE: Bioorganic & Medicinal Chemistry Letters (2003), 13(24), 4415-4419
CODEN: BMCLE8; ISSN: 0960-894X
PUBLISHER: Elsevier Science B.V.

DOCUMENT TYPE: Journal
LANGUAGE: English
AB Original **cyclosporin** A (CsA) derivs. bearing various alkylthio side chains at the sarcosine residue 3 (R configuration) and for the most potent and selective compds. a 4'-hydroxyl group at the Me-Leucine residue 4 were prepared in one or two steps from com. available CsA. The [2-(di-Me or diethylamino)-ethylthio-Sar]3-[(4'-OH)MeLeu]4-CsA derivs. displayed potent in vitro anti-HIV-1 (IC50 .apprx.46 nM) and low immunosuppressive activities (IC50≥1500 nM).
IT **210758-97-7P 210759-10-7P 227937-33-9P 227937-34-0P 227937-35-1P 653586-08-4P**
RL: BPN (Biosynthetic preparation); BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(preparation of non-immunosuppressive cyclophilin-Binding **cyclosporin** A derivs. as potential anti-HIV-1 drugs)
IT **151436-10-1P 210760-75-1P 210760-77-3P 210760-78-4P 227937-28-2P 227937-30-6P 653585-99-0P 653586-01-7P**
RL: BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(preparation of non-immunosuppressive cyclophilin-Binding **cyclosporin** A derivs. as potential anti-HIV-1 drugs)
IT **108466-76-8P 227937-26-0P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of non-immunosuppressive cyclophilin-Binding **cyclosporin** A derivs. as potential anti-HIV-1 drugs)
REFERENCE COUNT: 39 THERE ARE 39 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 6 OF 21 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2002:888508 HCAPLUS
DOCUMENT NUMBER: 137:389029
TITLE: Use of 3-position **cyclosporin** derivatives for hair growth
INVENTOR(S): Kim, Sang-Nyun; Ahn, Ho-Jeong; Lee, Chang-Woo; Lee, Min-Ho; Kim, Jung-Hun; Kim, Jong-Il; Kim, Seung-Jin; Cho, Ho-Song; Lee, Heon-Sik; Kim, Hyung-Jin
PATENT ASSIGNEE(S): LG Household & Health Care Ltd., S. Korea
SOURCE: PCT Int. Appl., 52 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002092032	A1	20021121	WO 2002-KR879	20020511
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
KR 2002086041	A	20021118	KR 2001-25682	20010511
EP 1387660	A1	20040211	EP 2002-728237	20020511
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
BR 2002009619	A	20040330	BR 2002-9619	20020511

JP 2004530685	T2	20041007	JP 2002-588951	20020511
US 2003207798	A1	20031106	US 2002-303281	20021125
US 6762164	B2	20040713		
PRIORITY APPLN. INFO.:			KR 2001-25682	A 20010511
			US 2002-141723	A3 20020509
			WO 2002-KR879	W 20020511

OTHER SOURCE(S): MARPAT 137:389029

AB The present invention discloses a hair growth promoting agent comprising a **cyclosporin** derivative as an active ingredient, and more particularly, a hair growth promoting agent comprising a **cyclosporin** A derivative substituted in the 3-position as an active ingredient. [N-methyl-D-Abu3] **cyclosporin** A was prepared by alkylation of **cyclosporin** A with EtI and the compound formulated in a hair tonic.

IT **108466-62-2P**
RL: COS (Cosmetic use); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(use of 3-position **cyclosporin** derivs. for hair growth)

REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 7 OF 21 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2002:195881 HCAPLUS
DOCUMENT NUMBER: 136:337615
TITLE: Calcineurin is essential for survival during membrane stress in Candida albicans
AUTHOR(S): Cruz, M. Cristina; Goldstein, Alan L.; Blankenship, Jill R.; Del Poeta, Maurizio; Davis, Dana; Cardenas, Maria E.; Perfect, John R.; McCusker, John H.; Heitman, Joseph
CORPORATE SOURCE: Department of Genetics, Duke University Medical Center, Durham, NC, 27710, USA
SOURCE: EMBO Journal (2002), 21(4), 546-559
CODEN: EMJODG; ISSN: 0261-4189
PUBLISHER: Oxford University Press
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The immunosuppressants **cyclosporin** A (CsA) and FK506 inhibit the protein phosphatase calcineurin and block T-cell activation and transplant rejection. Calcineurin is conserved in microorganisms and plays a general role in stress survival. CsA and FK506 are toxic to several fungi, but the common human fungal pathogen Candida albicans is resistant. However, combination of either CsA or FK506 with the antifungal drug fluconazole that perturbs synthesis of the membrane lipid ergosterol results in potent, synergistic fungicidal activity. Here we show that the C. albicans FK506 binding protein FKBP12 homolog is required for FK506 synergistic action with fluconazole. A mutation in the calcineurin B regulatory subunit that confers dominant FK506 resistance (CNB1-1/CNBI) abolished FK506-fluconazole synergism. Candida albicans mutants lacking calcineurin B (cnb1/cnbI) were found to be viable and markedly hypersensitive to fluconazole or membrane perturbation with SDS. FK506 was synergistic with fluconazole against azole-resistant C.albicans mutants, against other Candida species, or when combined with different azoles. We propose that calcineurin is part of a membrane stress survival pathway that could be targeted for therapy.

IT **108466-73-5**
RL: PAC (Pharmacological activity); BIOL (Biological study)
(synergistic action with fluconazole against Candida albicans)

REFERENCE COUNT: 95 THERE ARE 95 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 8 OF 21 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2000:11455 HCAPLUS
DOCUMENT NUMBER: 132:175375

TITLE: Immunosuppressive and nonimmunosuppressive **cyclosporine** analogs are toxic to the opportunistic fungal pathogen Cryptococcus neoformans via cyclophilin-dependent inhibition of calcineurin

AUTHOR(S): Cruz, M. Cristina; Del Poeta, Maurizio; Wang, Ping; Wenger, Roland; Zenke, Gerhard; Quesniaux, Valerie F. J.; Movva, N. Rao; Perfect, John R.; Cardenas, Maria E.; Heitman, Joseph

CORPORATE SOURCE: Department of Genetics, Durham, NC, 27710, USA

SOURCE: Antimicrobial Agents and Chemotherapy (2000), 44(1), 143-149
CODEN: AMACCQ; ISSN: 0066-4804

PUBLISHER: American Society for Microbiology

DOCUMENT TYPE: Journal

LANGUAGE: English

AB **Cyclosporine** (CsA) is an immunosuppressive and antimicrobial drug which, in complex with cyclophilin A, inhibits the protein phosphatase calcineurin. We recently found that Cryptococcus neoformans growth is resistant to CsA at 24° but sensitive at 37° and that calcineurin is required for growth at 37° and pathogenicity. Here CsA analogs were screened for toxicity against C. neoformans in vitro. In most cases, antifungal activity was correlated with cyclophilin A binding in vitro and inhibition of the mixed-lymphocyte reaction and interleukin 2 production in cell culture. Two unusual nonimmunosuppressive CsA derivs., (γ-OH) MeLeu4-Cs (211-810) and D-Sar (α-SMe)3 Val2-DH-Cs (209-825), which are also toxic to C. neoformans were identified. These CsA analogs inhibit C. neoformans via fungal cyclophilin A and calcineurin homologs. Our findings identify calcineurin as a novel antifungal drug target and suggest nonimmunosuppressive CsA analogs warrant investigation as antifungal agents.

IT **108466-73-5**, SDZ 209-825
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**cyclosporine** analogs are toxic to Cryptococcus neoformans via cyclophilin-dependent inhibition of calcineurin)

REFERENCE COUNT: 63 THERE ARE 63 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 9 OF 21 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 1999:819403 HCAPLUS
DOCUMENT NUMBER: 132:36039

TITLE: Preparation of **cyclosporin** derivatives via deprotonation reaction

INVENTOR(S): Viskov, Christian
PATENT ASSIGNEE(S): Rhone-Poulenc Rorer SA, Fr.

SOURCE: PCT Int. Appl., 46 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: French

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9967280	A1	19991229	WO 1999-FR1480	19990621

W: AE, AL, AU, BA, BB, BG, BR, CA, CN, CU, CZ, EE, GD, GE, HR, HU, ID, IL, IN, IS, JP, KP, KR, LC, LK, LR, LT, LV, MG, MK, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, SL, TR, TT, UA, US, UZ, VN, YU, ZA, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

FR 2780061	A1	19991224	FR 1998-7846		19980622
FR 2780061	B1	20010907			
AU 9942700	A1	20000110	AU 1999-42700		19990621
EP 1098903	A1	20010516	EP 1999-957167		19990621
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE, FI					
JP 2002518519	T2	20020625	JP 2000-555931		19990621
US 2001025025	A1	20010927	US 2000-742008		20001222
PRIORITY APPLN. INFO.:			FR 1998-7846	A	19980622
			WO 1999-FR1480	W	19990621

OTHER SOURCE(S): CASREACT 132:36039; MARPAT 132:36039

AB The invention concerns a novel method for preparing an intermediate polyanion for preparing **cyclosporin** derivs. by treating a **cyclosporin** with a hexamethyldisilazane metal salt, optionally in the presence of a metal halide. The treated **cyclosporin** has one or several free hydroxy groups and/or non-methylated nitrogen atoms in position α and/or any other acid group capable of deprotonation which are optionally deprotonated or in protected form. Thus, [(R)-2-(N,N-dimethylamino)ethylthio-Sar]3 **cyclosporine** A was prepared in 53 % yield via coupling of **cyclosporine** A with di-[2-(N,N-dimethylamino)ethyl] disulfide in presence of hexamethyldisilazane lithium salt and cesium chloride in tert-butylmethyl ether and toluene.

IT **210758-97-7P 210759-10-7P 227937-27-1P**
RL: BPN (Biosynthetic preparation); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(preparation of **cyclosporin** derivs. via coupling and deprotonation reactions)

REFERENCE COUNT: 8 THERE ARE 8 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

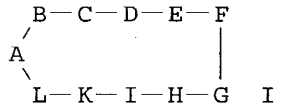
L8 ANSWER 10 OF 21 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 1999:811267 HCAPLUS
DOCUMENT NUMBER: 132:50254
TITLE: Preparation of novel **cyclosporins**
INVENTOR(S): Ellmerer-Mueller, Ernst; Brossner, Dagmar; Maslouh, Najib; Ambrosi, Horst-Dieter; Jas, Gerhard
PATENT ASSIGNEE(S): C-Chem A.-G., Switz.
SOURCE: PCT Int. Appl., 54 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9965933	A1	19991223	WO 1999-EP4012	19990610
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
CA 2334730	AA	19991223	CA 1999-2334730	19990610
AU 9948993	A1	20000105	AU 1999-48993	19990610
AU 760168	B2	20030508		
EP 1086124	A1	20010328	EP 1999-932697	19990610
EP 1086124	B1	20031119		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE, FI				
BR 9911160	A	20010403	BR 1999-11160	19990610
JP 2002518406	T2	20020625	JP 2000-554758	19990610
AT 254630	E	20031215	AT 1999-932697	19990610

PT 1086124	T	20040430	PT 1999-932697		19990610
ES 2212583	T3	20040716	ES 1999-932697		19990610
NO 2000006282	A	20010212	NO 2000-6282		20001211
US 6583265	B1	20030624	US 2001-701542		20010108
PRIORITY APPLN. INFO.:			EP 1998-110761	A	19980612
			WO 1999-EP4012	W	19990610

OTHER SOURCE(S): MARPAT 132:50254
GI



AB Compds. I [A = L-α-N-methylamino-β-hydroxy acid residue; B = α-aminobutyric acid, norvaline, threonine, or valine residue; C = substituted sarcosine residue; D = N-methyleucine, γ-hydroxy-N-methylleucine, N-methylvaline, or N-methylisoleucine residue; E = valine residue; F = N-methylleucine residue; G = alanine residue; H = Gly, D-alanine, D-serine, or O-hydroxyethyl-D-serine residue; I, K = N-methylleucine residue; L = N-methylvaline residue] were prepared Thus, 3-(pyridyl-2-thio)**cyclosporin** was prepared by treatment of **cyclosporin** A with 2,2'-dipyridyl disulfide and showed IC50 = 0.2 ng/mL for binding of cyclophilin.

IT **108506-88-3P 151436-10-1P 252731-33-2P**
252731-34-3P 252731-35-4P 252731-36-5P
252731-37-6P 252731-38-7P 252731-39-8P
252731-40-1P 252731-50-3P 252731-66-1P
252731-67-2P 252731-68-3P 252760-03-5P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of novel **cyclosporins**)

REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 11 OF 21 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1999:425790 HCAPLUS
DOCUMENT NUMBER: 131:59141
TITLE: Preparation of **cyclosporins** modified in position 3 via polyanions and coupling reaction
INVENTOR(S): Amouret, Guy; Guerreiro, Antonio; Viskov, Christian; Mignani, Serge; Evers, Michel; Barriere, Jean-Claude; Bashiardes, Georges; Carry, Jean-Christophe; Filoche, Bruno
PATENT ASSIGNEE(S): Rhone-Poulenc Rorer S.A., Fr.
SOURCE: PCT Int. Appl., 62 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: French
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9932512	A1	19990701	WO 1998-FR2745	19981216

W: AL, AU, BA, BB, BG, BR, CA, CN, CU, CZ, EE, GD, GE, HR, HU, ID, IL, IN, IS, JP, KP, KR, LC, LK, LR, LT, LV, MG, MK, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, SL, TR, TT, UA, US, UZ, VN, YU, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

FR 2772768	A1	19990625	FR 1997-16189	19971219
FR 2772768	B1	20000114		
ZA 9811531	A	19990615	ZA 1998-11531	19981215
AU 9917640	A1	19990712	AU 1999-17640	19981216
EP 1040121	A1	20001004	EP 1998-962475	19981216
EP 1040121	B1	20040721		

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE, FI

JP 2002502803	T2	20020129	JP 2000-525449	19981216
AT 271563	E	20040815	AT 1998-962475	19981216

PRIORITY APPLN. INFO.: FR 1997-16189 A 19971219
WO 1998-FR2745 W 19981216

OTHER SOURCE(S): CASREACT 131:59141; MARPAT 131:59141

AB The invention concerns a novel method for preparing a polyanion useful for preparing **cyclosporin** derivs. modified in position 3 by treating a **cyclosporin** with an alkali amide in liquid ammonia or in an aliphatic amine of low mol. weight, in the presence of a cosolvent, and optionally in the presence of dimethylpropyleneurea (DMPU). The treated **cyclosporin** has one or several free hydroxy groups and/or non-methylated nitrogen atoms in position α and/or any other acid group capable of being subjected to deprotonation and which are optionally subjected to deprotonation, or are in protected form. Thus, [(R)-2-(N-methyl-N-tert-butylamino)ethylthio-Sar]3-[4'-hydroxy-MeLeu]4-**cyclosporin** A was prepared via coupling of [4'-hydroxy-MeLeu]4-**cyclosporin** A with di-[2-(N,N-diethylamino)ethyl] disulfide in t-butylmethylether.

IT **108466-76-8P 210758-97-7P 210759-10-7P**
227937-27-1P 227937-28-2P 227937-30-6P
227937-32-8P 227937-33-9P 227937-34-0P
227937-35-1P
RL: IMF (Industrial manufacture); SPN (Synthetic preparation); PREP (Preparation)
(preparation of **cyclosporins** modified in position 3 via polyanions and coupling reaction)

IT **210760-77-3P 227937-26-0P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of **cyclosporins** modified in position 3 via polyanions and coupling reaction)

REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 12 OF 21 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1998:721724 HCAPLUS
DOCUMENT NUMBER: 130:4088
TITLE: Preparation of novel **cyclosporin** derivatives and pharmaceutical compositions
INVENTOR(S): Evers, Michel; Mignani, Serge; Carry, Jean-Christophe; Filoche, Bruno; Bashiardes, Georges; Bensoussan, Claude; Gueguen, Jean-Christophe; Barriere, Jean-Claude
PATENT ASSIGNEE(S): Rhone-Poulenc Rorer S.A., Fr.
SOURCE: PCT Int. Appl., 61 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: French
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

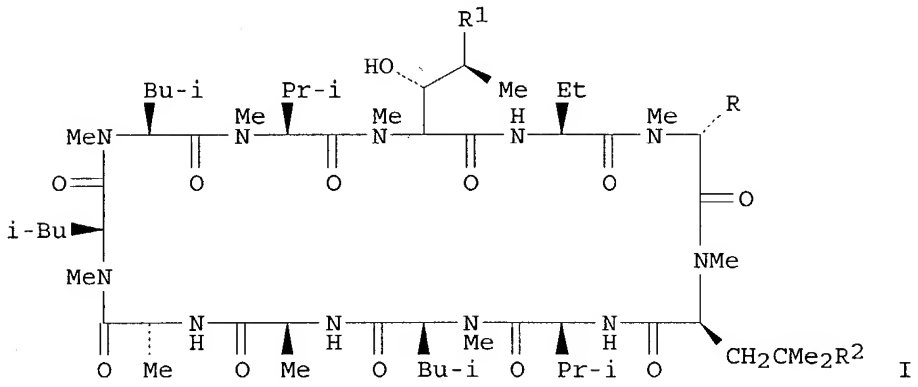
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE

WO 9849193		A1	19981105	WO 1998-FR838	19980427
W:	AL, AU, BA, BB, BG, BR, CA, CN, CU, CZ, EE, GE, GW, HU, ID, IL, IS, JP, KP, KR, LC, LK, LR, LT, LV, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, SL, TR, TT, UA, US, UZ, VN, YU, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW:	GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
FR 2762843		A1	19981106	FR 1997-5351	19970430
FR 2762843		B1	19991210		
AU 9875357		A1	19981124	AU 1998-75357	19980427
EP 979244		A1	20000216	EP 1998-922872	19980427
R:	AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE, FI				
JP 2001524105		T2	20011127	JP 1998-546664	19980427
ZA 9803618		A	19981104	ZA 1998-3618	19980429
US 5977067		A	19991102	US 1998-69959	19980430

PRIORITY APPLN. INFO.: FR 1997-5351 A 19970430
WO 1998-FR838 W 19980427

OTHER SOURCE(S): MARPAT 130:4088

GI



I

AB **Cyclosporin** derivs. I [R = H, MeS, alkyl, cycloalkyl or hydroxy-, carboxy-, alkoxycarbonyl-, or aminoalkyl or -cycloalkyl; R1 = alkylthiomethyl or R3CH2CH:CHCH2, where R3 = (un)substituted alkylthio, pyrimidinylthio, thiazolylthio, N-alkylimidazolylthio, hydroxyalkylphenylthio, hydroxyalkylphenoxy, nitrophenylamino, 2-oxo-1-pyrimidinyl; R2 = H, OH] were prepared and pharmaceutical compns. containing them described. Thus, [(3R,4R)-3-hydroxy-5-methylthio-N-methyl-L-leucine]1[(2R)-methylthiosarcosine]3-**cyclosporin** A was prepared by treating [(3R,4R)-3-hydroxy-5-methylthio-N-methyl-L-leucine]1-**cyclosporin** A with 1,3-dimethyltetrahydropyrimidin-2(1H)-one.

IT **215532-02-8P 215532-03-9P 215532-04-0P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of novel **cyclosporin** derivs. and pharmaceutical compns.)

IT **215531-93-4P 215531-94-5P 215531-96-7P 215531-97-8P 215531-98-9P**
RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of novel **cyclosporin** derivs. and pharmaceutical compns.)

REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS

RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

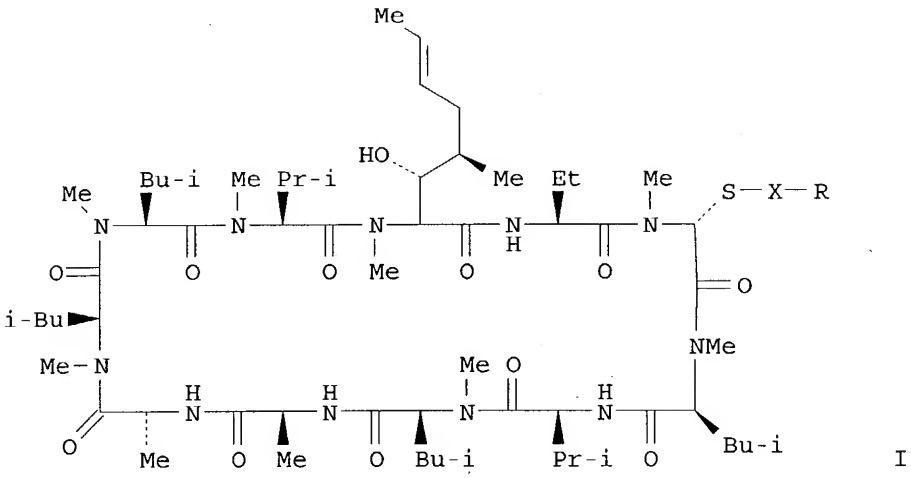
L8 ANSWER 13 OF 21 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1998:711235 HCAPLUS
DOCUMENT NUMBER: 130:90080
TITLE: X-ray structures and analysis of 11 **cyclosporin** derivatives complexed with cyclophilin A
AUTHOR(S): Kallen, Joerg; Mikol, Vincent; Taylor, Paul; Walkinshaw, Malcolm D.
CORPORATE SOURCE: Structural Biochemistry Group, The University of Edinburgh, Edinburgh, EH9 3JR, UK
SOURCE: Journal of Molecular Biology (1998), 283(2), 435-449
CODEN: JMOBAK; ISSN: 0022-2836
PUBLISHER: Academic Press
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Eight new x-ray structures of different cyclophilin A/**cyclosporin** -derivative complexes are presented. These structures, combined with the existing three published **cyclosporin** complexes, provide a useful structural database for the anal. of protein-ligand interactions. The effect of small chemical differences on protein-ligand hydrogen-bonding, van der Waals interactions and water structure is presented. (c) 1998 Academic Press.
IT **108466-60-0 108466-73-5**
RL: BPR (Biological process); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study); PROC (Process)
(X-ray structures and anal. of 11 **cyclosporin** derivs. complexed with cyclophilin A)
REFERENCE COUNT: 52 THERE ARE 52 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 14 OF 21 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1998:561743 HCAPLUS
DOCUMENT NUMBER: 129:149255
TITLE: Preparation of **cyclosporin** derivatives and their pharmaceutical compositions
INVENTOR(S): Barriere, Jean Claude; Carry, Jean Christophe; Filoche, Bruno; Evers, Michel; Bashiardes, Georges; Mignani, Serge; Leconte, Jean Pierre
PATENT ASSIGNEE(S): Rhone-Poulenc Rorer SA, Fr.
SOURCE: Fr. Demande, 21 pp.
CODEN: FRXXBL
DOCUMENT TYPE: Patent
LANGUAGE: French
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
FR 2757522	A1	19980626	FR 1996-15956	19961224
FR 2757522	B1	19990129		
ZA 9711606	A	19980625	ZA 1997-11606	19971223
WO 9828329	A1	19980702	WO 1997-FR2405	19971223
W: AL, AU, BA, BB, BG, BR, CA, CN, CU, CZ, EE, GE, GH, GW, HU, ID, IL, IS, JP, KP, KR, LC, LK, LR, LT, LV, MG, MK, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, SL, TR, TT, UA, US, UZ, VN, YU, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
AU 9856692	A1	19980717	AU 1998-56692	19971223
US 5965527	A	19991012	US 1997-996699	19971223

EP 948527	A1	19991013	EP 1997-952998	19971223
EP 948527	B1	20020605		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE, FI				
JP 2001507346	T2	20010605	JP 1998-528489	19971223
AT 218580	E	20020615	AT 1997-952998	19971223
PT 948527	T	20021129	PT 1997-952998	19971223
ES 2178037	T3	20021216	ES 1997-952998	19971223
PRIORITY APPLN. INFO.:			FR 1996-15956	A 19961224
			WO 1997-FR2405	W 19971223

OTHER SOURCE(S): MARPAT 129:149255
GI



I

AB **Cyclosporin** derivs. I (X = alkylene or cycloalkylene; R = CO2H, carbalkoxy, NR1R2, where R1 and R2 are H, alkyl, cycloalkyl, substituted Ph, benzyl, heterocyclyl or R1R2N = heterocyclyl) were prepared for use in pharmaceutical compns. optionally associated with an antiviral, immunomodulator, or antimicrobial agent. Thus, treatment of **cyclosporin** A with bis[2-(diethylamino)ethyl] disulfide afforded I (X = ethylene, R = Et).

IT **210760-75-1P 210760-76-2P 210760-77-3P 210760-78-4P**
RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of **cyclosporin** derivs. and their pharmaceutical compns.)

L8 ANSWER 15 OF 21 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER:	1998:561742 HCAPLUS
DOCUMENT NUMBER:	129:149254
TITLE:	Preparation of **cyclosporin** derivatives and their pharmaceutical compositions
INVENTOR(S):	Barriere, Jean Claude; Carry, Jean Christophe; Filoche, Bruno; Evers, Michel; Bashiardes, Georges; Mignani, Serge
PATENT ASSIGNEE(S):	Rhone-Poulenc Rorer SA, Fr.
SOURCE:	Fr. Demande, 22 pp. CODEN: FRXXBL
DOCUMENT TYPE:	Patent
LANGUAGE:	French
FAMILY ACC. NUM. COUNT:	1

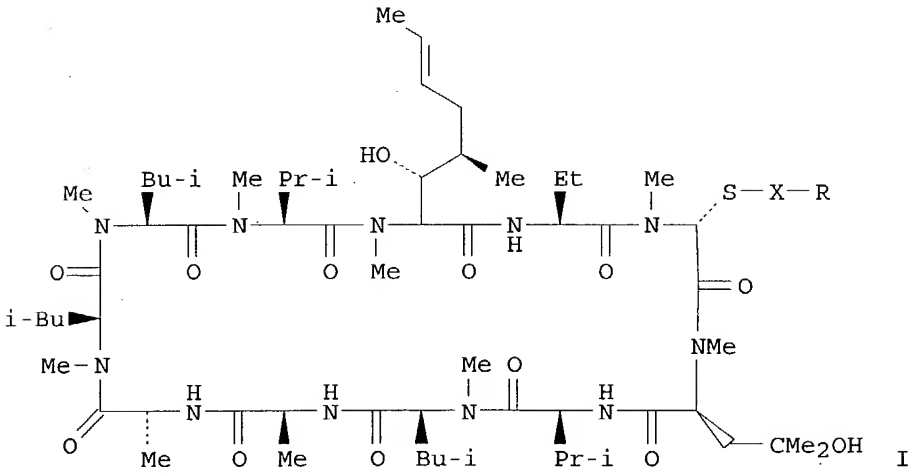
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
FR 2757521	A1	19980626	FR 1996-15955	19961224
FR 2757521	B1	19990129		
ZA 9711607	A	19980624	ZA 1997-11607	19971223
WO 9828330	A1	19980702	WO 1997-FR2406	19971223
W: AL, AU, BA, BB, BG, BR, CA, CN, CU, CZ, EE, GE, GH, GW, HU, ID, IL, IS, JP, KP, KR, LC, LK, LR, LT, LV, MG, MK, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, SL, TR, TT, UA, US, UZ, VN, YU, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
AU 9856693	A1	19980717	AU 1998-56693	19971223
EP 951474	A1	19991027	EP 1997-952999	19971223
EP 951474	B1	20020605		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE, FI				
US 5994299	A	19991130	US 1997-997612	19971223
JP 2001507347	T2	20010605	JP 1998-528490	19971223
AT 218582	E	20020615	AT 1997-952999	19971223
PT 951474	T	20021129	PT 1997-952999	19971223
ES 2178038	T3	20021216	ES 1997-952999	19971223

PRIORITY APPLN. INFO.: FR 1996-15955 A 19961224
WO 1997-FR2406 W 19971223

OTHER SOURCE(S): MARPAT 129:149254

GI



I

AB **Cyclosporin** derivs. I (X = alkylene or cycloalkylene; R = OH, CO2H, carbalkoxy, NR1R2, where R1 and R2 are H, alkyl, cycloalkyl, substituted Ph, benzyl, heterocyclyl or R1R2N = heterocyclyl) were prepared for use in pharmaceutical compns. optionally associated with an antiviral, immunomodulator, or antimicrobial agent. Thus, treatment of 4'-hydroxy-4-MeLeu **cyclosporin** with bis[2-(dimethylamino)ethyl] disulfide afforded I (X = ethylene, R = Me).

IT **210759-10-7P**
RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of **cyclosporin** derivs. and their pharmaceutical

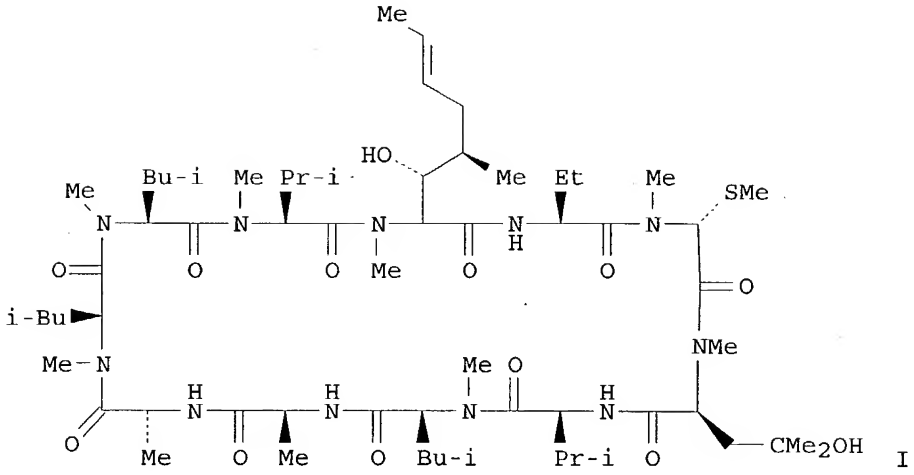
compns.)

L8 ANSWER 16 OF 21 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1998:561741 HCAPLUS
DOCUMENT NUMBER: 129:149253
TITLE: Preparation of **cyclosporin** derivatives and their pharmaceutical compositions
INVENTOR(S): Barriere, Jean Claude; Carry, Jean Christophe; Filoche, Bruno; Evers, Michel; Bashiardes, Georges; Mignani, Serge
PATENT ASSIGNEE(S): Rhone-Poulenc Rorer SA, Fr.
SOURCE: Fr. Demande, 11 pp.
CODEN: FRXXBL
DOCUMENT TYPE: Patent
LANGUAGE: French
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
FR 2757520	A1	19980626	FR 1996-15954	19961224
FR 2757520	B1	19990129		
WO 9828328	A1	19980702	WO 1997-FR2404	19971223
W: AL, AU, BA, BB, BG, BR, CA, CN, CU, CZ, EE, GE, GH, GW, HU, ID, IL, IS, JP, KP, KR, LC, LK, LR, LT, LV, MG, MK, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, SL, TR, TT, UA, US, UZ, VN, YU, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
AU 9856691	A1	19980717	AU 1998-56691	19971223
US 5948755	A	19990907	US 1997-997613	19971223
EP 951473	A1	19991027	EP 1997-952997	19971223
EP 951473	B1	20020605		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE, FI				
JP 2001507016	T2	20010529	JP 1998-528488	19971223
AT 218581	E	20020615	AT 1997-952997	19971223
PT 951473	T	20021129	PT 1997-952997	19971223
ES 2178036	T3	20021216	ES 1997-952997	19971223

PRIORITY APPLN. INFO.: FR 1996-15954 A 19961224
WO 1997-FR2404 W 19971223

GI



I

AB **Cyclosporin** derivative I was prepared by treating 4'-hydroxy-4-MeLeu **cyclosporin** with Me2S. Pharmaceutical compns. are described which contain I, optionally in association with an antiviral, immunomodulator, or antimicrobial agent.

IT **210758-97-7P**
RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of **cyclosporin** derivs. and their pharmaceutical compns.)

L8 ANSWER 17 OF 21 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1995:51474 HCAPLUS
DOCUMENT NUMBER: 122:45734
TITLE: Roles of peptidyl-prolyl cis-trans isomerase and calcineurin in the mechanisms of antimalarial action of **cyclosporin** A, FK506, and rapamycin
AUTHOR(S): Bell, Angus; Wernli, Barbara; Franklin, Richard M.
CORPORATE SOURCE: Dep. Structural Biology, Univ. Basal, Basel, CH-4056, Switz.
SOURCE: Biochemical Pharmacology (1994), 48(3), 495-503
CODEN: BCPCA6; ISSN: 0006-2952
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The immunosuppressive peptide **cyclosporin** A inhibits the growth of malaria parasites in vitro and in vivo, but little is known about its mechanism of antimalarial action. The immunosuppressive action of **cyclosporin** A is believed to result from binding of the drug to cytophilins (intracellular peptidyl-prolyl cis-trans isomerases), and inhibition of the protein phosphatase calcineurin by the **cyclosporin** A-cyclophilin complex. Two immunosuppressive macrolides, FK506 and rapamycin, bind to a distinct isomerase, FKBP12, and the FK506-FKBP complex also inhibits calcineurin. Calcineurin itself is apparently involved in signal transduction between the T-cell membrane and nucleus, and its inhibition blocks T-cell activation. Rapamycin inhibits a later step in T-cell proliferation. Peptidylprolyl cis-trans isomerase activity was detected in exts. of Plasmodium falciparum. It was completely inhibited by concns. of **cyclosporin** A above 0.1 μM, but not by FK506 or rapamycin, and probably represented one or more cyclophilins. Comparison of the antimalarial and anti-isomerase activities of a series of **cyclosporin** analogs failed to reveal a correlation between the two properties. **Cyclosporin** A and its more active 8'-oxymethyl-dihydro-derivative, in combination with the

cyclophilin-containing P. falciparum extract inhibited the protein phosphatase activity of bovine calcineurin. Therefore inhibition of a putative P. falciparum calcineurin by a complex of CsA and cyclophilin might be responsible for the antimalarial action of the drug. The most active **cyclosporin**, however, was a 3'-keto-derivative of **cyclosporin** D (SDZ PSC-833) which inhibited P. falciparum growth with a 50% inhibitory concns. (IC50) of 0.032 μM (compared with 0.30 μM for **cyclosporin** A), but was a poor inhibitor of the parasite isomerase. 3'-Keto-**cyclosporin** D has negligible immunosuppressive activity, but it strongly inhibits the P-glycoprotein of multi-drug resistant mammalian tumor cells. FK506 and rapamycin were also active antimalarials (IC50 of 1.9 and 2.6 μM, resp.) but in the absence of detectable FKBP in P. falciparum exts., their mechanisms of antimalarial action remain unclear.

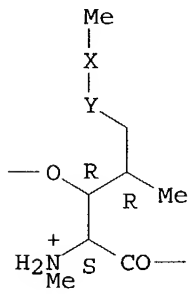
IT **159992-08-2**
RL: BIOL (Biological study)
(peptidyl-prolyl cis-trans isomerase inhibition by, antimalarial activity in relation to)

L8 ANSWER 18 OF 21 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1994:135131 HCAPLUS
DOCUMENT NUMBER: 120:135131
TITLE: Preparation of iso-**cyclosporin** salts as drugs
INVENTOR(S): Wenger, Roland
PATENT ASSIGNEE(S): Sandoz-Erfindungen Verwaltungsgesellschaft m.b.H., Austria; Sandoz-Patent-G.m.b.H.; Sandoz Ltd.
SOURCE: PCT Int. Appl., 28 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9317039	A1	19930902	WO 1993-EP407	19930220
W: AU, CA, CZ, FI, HU, JP, KR, NO, NZ, PL, RU, SK, UA, US				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
AU 9336295	A1	19930913	AU 1993-36295	19930220
PRIORITY APPLN. INFO.:			GB 1992-3886 A	19920224
			WO 1993-EP407 A	19930220

OTHER SOURCE(S): MARPAT 120:135131
GI

Q=



AB Title compds., containing residue Q (XY = trans-CH:CH, CH2CH2) at position 1, were prepared Thus, (D-Ser)8-**cyclosporin** was stirred for 66 h

with CF3CO2H in PhMe to give, after workup and salification, (iso-MeBmt)1(D-Ser)8-**cyclosporin** hydrochloride (iso-MeBmt = Q where XY = trans-CH:CH). Title compds. were active in Freund's adjuvant arthritis test in rats at 14-25 mg/kg orally, and were active in the kidney allograft reaction test in rats at 5-7.5 mg/kg orally. Title compds have reduced toxicity relative to **cyclosporins.**

IT **108466-73-5 152546-99-1**
RL: RCT (Reactant); RACT (Reactant or reagent)
(acid-catalyzed isomerization of, in prepn of drug)

IT **152546-97-9P 152546-98-0P 152614-93-2P 152614-94-3P**
RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of, as drug)

L8 ANSWER 19 OF 21 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1993:671687 HCAPLUS
DOCUMENT NUMBER: 119:271687
TITLE: Modification of **cyclosporin** A (CS): generation of an enolate at the sarcosine residue and reactions with electrophiles
AUTHOR(S): Seebach, Dieter; Beck, Albert K.; Bossler, Hans G.; Gerber, Christian; Ko, Soo Y.; Murtiashaw, C. William; Naef, Reto; Shoda, Shinichiro; Thaler, Adrian; et al.
CORPORATE SOURCE: Lab. Org. Chem., Eidg. Techn. Hochsch., Zurich, CH-8092, Switz.
SOURCE: Helvetica Chimica Acta (1993), 76(4), 1564-90
CODEN: HCACAV; ISSN: 0018-019X
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 119:271687

AB Strong bases (LDA or BuLi) convert **cyclosporin** A (CS) to a hexalithio derivative containing a Li alkoxide, four Li azaenolate, and one Li enolate unit. The Li6 compound is solubilized in THF by addition of excess LDA or LiCl. Reactions with electrophiles (alkyl halides, aldehydes, chloroformates, CO2, disulfides, D2O) at low temps. give products containing new side chains at the sarcosine residue of the cyclic undecapeptide in moderate to high yields and, with Re- or Si-selectivities of up to 7:1, depending upon the lithiation conditions. Pure CS derivs. can be isolated by column chromatog. N-alkylations or cleavage of the peptide backbone by carbonyl addition occur only at higher temps. and/or with prolonged reaction times. Very little or no epimerization of stereogenic centers occurs under the conditions employed. Possible reasons for the feasibility of these surprising conversions of CS are discussed. For comparison, [MeAla3]CS and [D-MeAla3]CS were also prepared by conventional peptide synthesis in solution Their 1H and 13C NMR spectra are compared with those of CS.

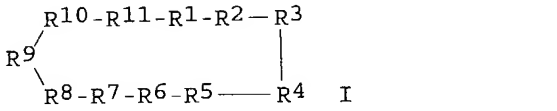
IT **108466-62-2P 108466-63-3P 108466-76-8P 108506-88-3P 151371-06-1P 151371-07-2P 151436-10-1P 151436-15-6P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of, via stereoselective alkylation of **cyclosporin** A enolate)

L8 ANSWER 20 OF 21 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1989:497726 HCAPLUS
DOCUMENT NUMBER: 111:97726
TITLE: New **cyclosporin** analogs with modified C-9-amino acids as immunosuppressants
INVENTOR(S): Witzel, Bruce W.
PATENT ASSIGNEE(S): Merck and Co., Inc., USA
SOURCE: Brit. UK Pat. Appl., 59 pp.
CODEN: BAXXDU

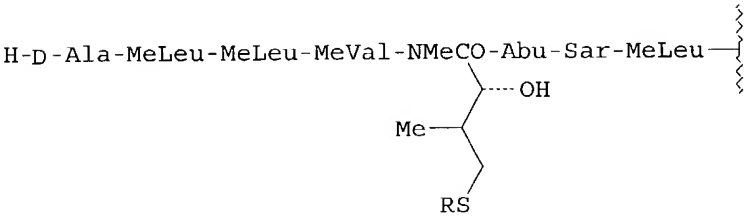
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

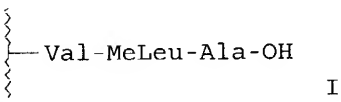
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
GB 2205317	A1	19881207	GB 1988-12273	19880524
US 4798823	A	19890117	US 1987-57196	19870603
US 4885276	A	19891205	US 1988-261868	19881024

PRIORITY APPLN. INFO.: US 1987-57196 A 19870603
OTHER SOURCE(S): CASREACT 111:97726; MARPAT 111:97726
GI



I





II

AB The title peptides [I; R1 = NR12CH[CH(OH)CHR13CH2XR]CO (Q), (4R)-4-[(E)-2-butenyl]-4-methyl-N-methyl-L-threonine residue; R = H, lower (halo)alkyl, lower alkenyl, (un)substituted aryl or heteroaryl, etc.; R12 = lower alkyl, lower alkylphenyl, aryl; R13 = lower alkyl; X = S, SO, SO2, O, MeLeuN; R2 = L-NHCHPrCO (Abu), Nva, Thr, R1; R3 = MeGly, NMeCH(SMe)CO, D-MeAla, MeAla, D-Pro; R4 = MeLeu; R5 = Val, Nval; R6 = MeLeu; R7 = Ala, Abu, Phe; R8 = D-Ala, Ala; R9 = MeLeu, MeVal; R10 = MeLeu, Leu; R11 = MeVal, Val, MeLeu, Abu] useful as immunosuppressants, were prepared by cyclization of linear undecapeptides (II). Reaction of (2R,3R)-3,4-isopropylidene-2-methyl-1-O-p-toluenesulfonyl-1,2,4-butanetriol with MeSNa in MeOH followed successively by deacetonation and selective benzoylation with BzCl gave (2R,3R)-MeSCH2CHMeCH(OH)CH2OBz which was etherified with EtOCH:CH2 in CH2Cl2 containing CF3CO2H and the resulting ether was saponified to give (2R,3R)-MeSCH2CHMeCH(OCHMeOEt)CH2OH. Oxidation of the latter with SO2-pyridine complex and Me2SO containing Et3N followed by hydrolysis gave (2R,3R)-MeSCH2CHMeCH(OH)CHO which underwent addition reaction with KCN and MeNH2.HCl in MeOH to give (2RS,3R,4R)-MeSCH2CHMeCH(OH)CH(CN)NHMe. Cyclocondensation of the latter with 1,1'-carbonyldiimidazole in CH2Cl2 gave 3-methyl-5-[1-methyl-2-(methylthio)ethyl]-2-oxooxazolidine-4-carbonitrile which was converted into Et oxooxazolidine-4-carboxylate derivative via Et oxooxazolidine-4-imidate. Hydrolysis of the carboxylate followed by saponification gave (2S,3R,4R)-MeSCH2CHMeCH(OH)CH(NHMe)CO2H (III). II (R = Me) was prepared by block synthesis of 1N,3O-isopropylidene derivative of III with 2 protected peptide fragments followed by deprotection and then cyclized to give I [R1

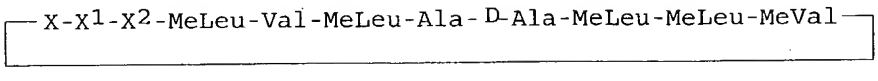
=(2S,3R,4R)-NHMeCH[CH(OH)CHMeCH2SMe]CO; R2 = Abu, R3 = MeGly, R4 = R6 = R9 = R10 = MeLeu; R5 = Val, R7 = Ala, R8 = D-Ala, R11 = MeVal]. In R. Handschumacher's cyclophilin binding assay, the latter showed 179% of **cyclosporin** A activity.

IT **122008-39-3P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of, as immunosuppressant)

L8 ANSWER 21 OF 21 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1987:407610 HCAPLUS
DOCUMENT NUMBER: 107:7610
TITLE: **Cyclosporins**
INVENTOR(S): Seebach, Dieter
PATENT ASSIGNEE(S): Sandoz A.-G., Switz.; Sandoz-Patent-G.m.b.H.; Sandoz-Erfindungen Verwaltungsgesellschaft m.b.H.
SOURCE: Eur. Pat. Appl., 66 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 194972	A2	19860917	EP 1986-810112	19860306
EP 194972	A3	19890712		
EP 194972	B1	19920729		
R: AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE				
AT 78832	E	19920815	AT 1986-810112	19860306
US 4703033	A	19871027	US 1986-837434	19860307
DK 8601094	A	19860912	DK 1986-1094	19860310
FI 8600993	A	19860912	FI 1986-993	19860310
JP 61212599	A2	19860920	JP 1986-53528	19860310
JP 07059594	B4	19950628		
HU 45272	A2	19880628	HU 1986-1009	19860310
ES 552855	A1	19890116	ES 1986-552855	19860310
ES 552855	A5	19890214		
HU 47137	A2	19890130	HU 1986-1434	19860310
PL 151029	B1	19900731	PL 1986-258350	19860310
PL 151429	B1	19900928	PL 1986-267785	19860310
AU 8654485	A1	19860918	AU 1986-54485	19860311
AU 588860	B2	19890928		
ZA 8601805	A	19871125	ZA 1986-1805	19860311
ES 557619	A1	19880716	ES 1987-557619	19870701
ES 557619	A5	19880816		
US 4771122	A	19880913	US 1987-103990	19871001
AU 8938176	A1	19891102	AU 1989-38176	19890717
PRIORITY APPLN. INFO.:			GB 1985-6230 A	19850311
			GB 1985-11029 A	19850501
			GB 1986-2370 A	19860131
			EP 1986-810112 A	19860306
			US 1986-837434 A3	19860307

GI



I

AB The title compds. I [X = (dihydro)-N-methyl-4-[(2E,4R)-but-2-en-1-yl]-4-methyl-L-threonyl (MeBmt); X1 = αAbu, Thr, Val, Nva; X2 = NMeCHRCO; R = halo, cyano, CONH2, (un)substituted alkyl, alkylcarbonyl, (un)substituted alkylthio, (un)substituted alkenyl, (hetero)arylthio, etc.], possessing immunosuppressive, antiinflammatory and antiparasitic activity, were prepared by treating **cyclosporins** with a base and reacting the resulting **cyclosporin** polyanions having a deprotonated sarcosine residue (I; X2 = sarcosyl) with electrophiles, e.g. aldehydes, isocyanates, disulfides, alkyl halides. Thus, **cyclosporin** A in THF was added dropwise to 6.7 equiv (Me2CH)2NLi in THF at -78° and after 1 h MeI was added at -78°. The mixture was allowed to warm to room temperature to give I (X = MeBmt; X1 = αAbu; X2 = MeAla). The title compds. at 0.01-10 μg/mL inhibited concanavalin A stimulated DNA synthesis, cell-proliferation and blasto-genesis in mouse spleen lymphocytes and at 1-30 mg/kg/day p.o. were active against arthritis in rats, and at 10-50 mg/kg/day p.o. doubled the survival time of mice infected with malaria.

IT **108466-60-0P 108466-61-1P 108466-62-2P**
108466-63-3P 108466-64-4P 108466-73-5P
108466-76-8P 108466-77-9P 108506-88-3P
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of, as immunosuppressive, antiinflammatory, and antiparasitic agent)

```
=> sel hit rn
E1 THROUGH E74 ASSIGNED

=> file reg
FILE 'REGISTRY' ENTERED AT 14:16:31 ON 03 DEC 2004
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
COPYRIGHT (C) 2004 American Chemical Society (ACS)

Property values tagged with IC are from the ZIC/VINITI data file
provided by InfoChem.

STRUCTURE FILE UPDATES:    1 DEC 2004  HIGHEST RN 791553-15-6
DICTIONARY FILE UPDATES:   1 DEC 2004  HIGHEST RN 791553-15-6

TSCA INFORMATION NOW CURRENT THROUGH MAY 21, 2004

  Please note that search-term pricing does apply when
  conducting SmartSELECT searches.

Crossover limits have been increased.  See HELP CROSSOVER for details.

Experimental and calculated property data are now available. For more
information enter HELP PROP at an arrow prompt in the file or refer
to the file summary sheet on the web at:
http://www.cas.org/ONLINE/DBSS/registryss.html

=> s e1-e74
             1 108466-62-2/BI
               (108466-62-2/RN)
             1 108466-73-5/BI
               (108466-73-5/RN)
             1 108466-76-8/BI
               (108466-76-8/RN)
             1 151436-10-1/BI
               (151436-10-1/RN)
             1 210758-97-7/BI
               (210758-97-7/RN)
```

1 210759-10-7/BI
(210759-10-7/RN)
1 210760-77-3/BI
(210760-77-3/RN)
1 108506-88-3/BI
(108506-88-3/RN)
1 108466-60-0/BI
(108466-60-0/RN)
1 108466-63-3/BI
(108466-63-3/RN)
1 210760-75-1/BI
(210760-75-1/RN)
1 210760-78-4/BI
(210760-78-4/RN)
1 215531-94-5/BI
(215531-94-5/RN)
1 227937-26-0/BI
(227937-26-0/RN)
1 227937-27-1/BI
(227937-27-1/RN)
1 227937-28-2/BI
(227937-28-2/RN)
1 227937-30-6/BI
(227937-30-6/RN)
1 227937-33-9/BI
(227937-33-9/RN)
1 227937-34-0/BI
(227937-34-0/RN)
1 227937-35-1/BI
(227937-35-1/RN)
1 108466-61-1/BI
(108466-61-1/RN)
1 108466-64-4/BI
(108466-64-4/RN)
1 108466-77-9/BI
(108466-77-9/RN)
1 122008-39-3/BI
(122008-39-3/RN)
1 151371-06-1/BI
(151371-06-1/RN)
1 151371-07-2/BI
(151371-07-2/RN)
1 151436-15-6/BI
(151436-15-6/RN)
1 152546-97-9/BI
(152546-97-9/RN)
1 152546-98-0/BI
(152546-98-0/RN)
1 152546-99-1/BI
(152546-99-1/RN)
1 152614-93-2/BI
(152614-93-2/RN)
1 152614-94-3/BI
(152614-94-3/RN)
1 159992-08-2/BI
(159992-08-2/RN)
1 210760-76-2/BI
(210760-76-2/RN)
1 215531-93-4/BI
(215531-93-4/RN)
1 215531-96-7/BI
(215531-96-7/RN)
1 215531-97-8/BI

(215531-97-8/RN)
1 215531-98-9/BI
(215531-98-9/RN)
1 215532-02-8/BI
(215532-02-8/RN)
1 215532-03-9/BI
(215532-03-9/RN)
1 215532-04-0/BI
(215532-04-0/RN)
1 227937-32-8/BI
(227937-32-8/RN)
1 252731-33-2/BI
(252731-33-2/RN)
1 252731-34-3/BI
(252731-34-3/RN)
1 252731-35-4/BI
(252731-35-4/RN)
1 252731-36-5/BI
(252731-36-5/RN)
1 252731-37-6/BI
(252731-37-6/RN)
1 252731-38-7/BI
(252731-38-7/RN)
1 252731-39-8/BI
(252731-39-8/RN)
1 252731-40-1/BI
(252731-40-1/RN)
1 252731-50-3/BI
(252731-50-3/RN)
1 252731-66-1/BI
(252731-66-1/RN)
1 252731-67-2/BI
(252731-67-2/RN)
1 252731-68-3/BI
(252731-68-3/RN)
1 252760-03-5/BI
(252760-03-5/RN)
1 653585-99-0/BI
(653585-99-0/RN)
1 653586-01-7/BI
(653586-01-7/RN)
1 653586-08-4/BI
(653586-08-4/RN)
1 674802-84-7/BI
(674802-84-7/RN)
1 676618-76-1/BI
(676618-76-1/RN)
1 683774-61-0/BI
(683774-61-0/RN)
1 683774-62-1/BI
(683774-62-1/RN)
1 683774-63-2/BI
(683774-63-2/RN)
1 683774-64-3/BI
(683774-64-3/RN)
1 683774-65-4/BI
(683774-65-4/RN)
1 683774-66-5/BI
(683774-66-5/RN)
1 683774-67-6/BI
(683774-67-6/RN)
1 683774-68-7/BI
(683774-68-7/RN)

1 683774-69-8/BI
(683774-69-8/RN)
1 683774-70-1/BI
(683774-70-1/RN)
1 683774-71-2/BI
(683774-71-2/RN)
1 683774-72-3/BI
(683774-72-3/RN)
1 683774-73-4/BI
(683774-73-4/RN)
1 683774-74-5/BI
(683774-74-5/RN)
L9 74 (108466-62-2/BI OR 108466-73-5/BI OR 108466-76-8/BI OR 151436-10-1/BI OR 210758-97-7/BI OR 210759-10-7/BI OR 210760-77-3/BI OR 108506-88-3/BI OR 108466-60-0/BI OR 108466-63-3/BI OR 210760-75-1/BI OR 210760-78-4/BI OR 215531-94-5/BI OR 227937-26-0/BI OR 227937-27-1/BI OR 227937-28-2/BI OR 227937-30-6/BI OR 227937-33-9/BI OR 227937-34-0/BI OR 227937-35-1/BI OR 108466-61-1/BI OR 108466-64-4/BI OR 108466-77-9/BI OR 122008-39-3/BI OR 151371-06-1/BI OR 151371-07-2/BI OR 151436-15-6/BI OR 152546-97-9/BI OR 152546-98-0/BI OR 152546-99-1/BI OR 152614-93-2/BI OR 152614-94-3/BI OR 159992-08-2/BI OR 210760-76-2/BI OR 215531-93-4/BI OR 215531-96-7/BI OR 215531-97-8/BI OR 215531-98-9/BI OR 215532-02-8/BI OR 215532-03-9/BI OR 215532-04-0/BI OR 227937-32-8/BI OR 252731-33-2/BI OR 252731-34-3/BI OR 252731-35-4/BI OR 252731-36-5/BI OR 252731-37-6/BI OR 252731-38-7/BI OR 252731-39-8/BI OR 252731-40-1/BI OR 252731-50-3/BI OR 252731-66-1/BI OR 252731-67-2/BI OR 252731-68-3/BI OR 252760-03-5/BI O

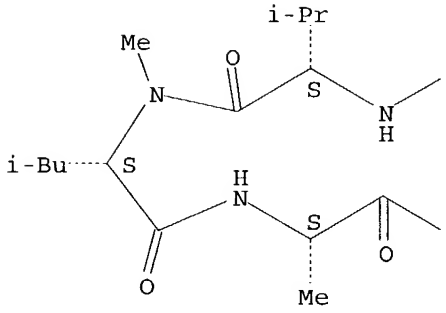
=> d ide can l9 1 5 10 15 20 25 30 35 40 45 50 55 60 65 70 74

L9 ANSWER 1 OF 74 REGISTRY COPYRIGHT 2004 ACS on STN
RN **683774-74-5** REGISTRY
CN Cyclosporin A, 8-[(2R)-2-[[(dimethylamino)thioxomethyl]dithio]-N-methylglycine]-, chloroacetate (ester) (9CI) (CA INDEX NAME)
FS PROTEIN SEQUENCE; STEREOSEARCH
MF C67 H117 Cl N12 O13 S3
SR CA
LC STN Files: CA, CAPLUS, USPATFULL
DT.CA CAplus document type: Patent
RL.P Roles from patents: BIOL (Biological study); PREP (Preparation); USES (Uses)

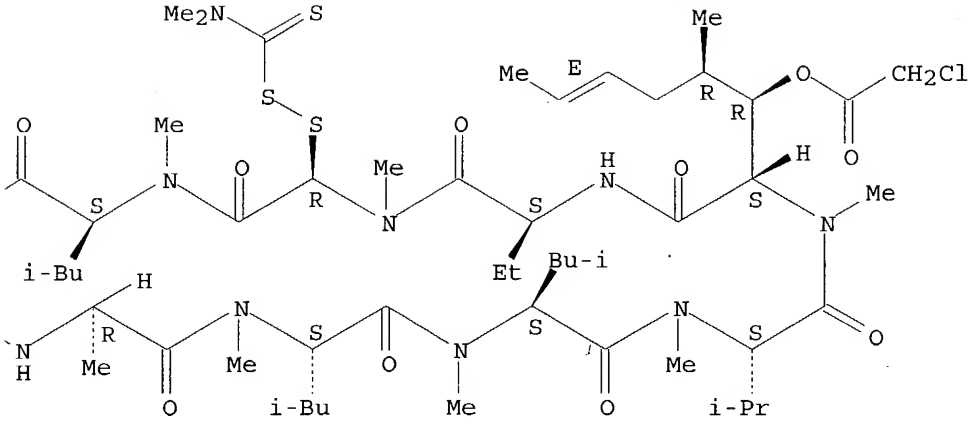
RELATED SEQUENCES AVAILABLE WITH SEQLINK

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



PAGE 1-B



1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

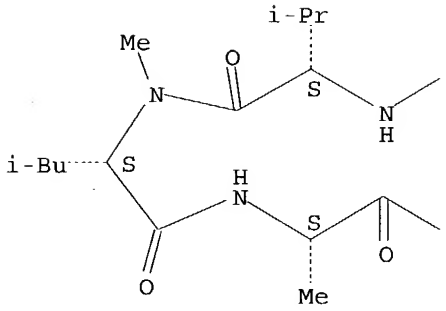
REFERENCE 1: 140:380253

L9 ANSWER 5 OF 74 REGISTRY COPYRIGHT 2004 ACS on STN
RN **683774-70-1** REGISTRY
CN Cyclosporin A, 8-[(2R)-N-methyl-2-[(1-methylethyl)thio]glycine]-, chloroacetate (ester) (9CI) (CA INDEX NAME)
FS PROTEIN SEQUENCE; STEREOSEARCH
MF C67 H118 Cl N11 O13 S
SR CA
LC STN Files: CA, CAPLUS, USPATFULL
DT.CA CAplus document type: Patent
RL.P Roles from patents: BIOL (Biological study); PREP (Preparation); USES (Uses)

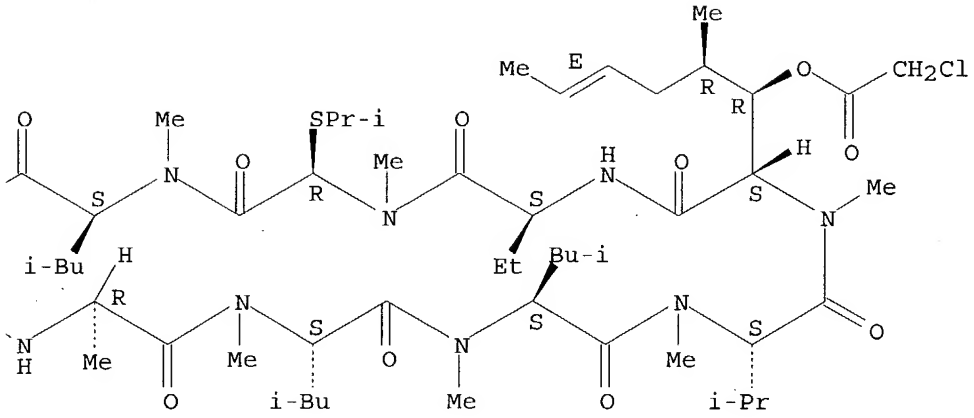
RELATED SEQUENCES AVAILABLE WITH SEQLINK

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



PAGE 1-B



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

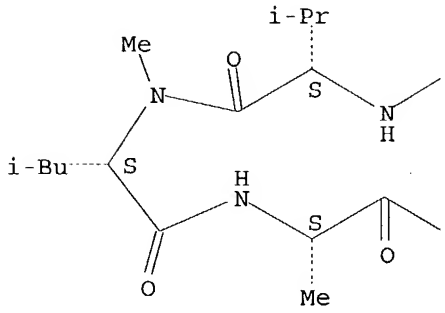
REFERENCE 1: 140:380253

L9 ANSWER 10 OF 74 REGISTRY COPYRIGHT 2004 ACS on STN
RN **683774-65-4** REGISTRY
CN Cyclosporin A, 8-[(2R)-N-methyl-2-[(phenylmethyl)thio]glycine]- (9CI) (CA INDEX NAME)
FS PROTEIN SEQUENCE; STEREOSEARCH
MF C69 H117 N11 O12 S
SR CA
LC STN Files: CA, CAPLUS, USPATFULL
DT.CA CAplus document type: Patent
RL.P Roles from patents: BIOL (Biological study); USES (Uses)

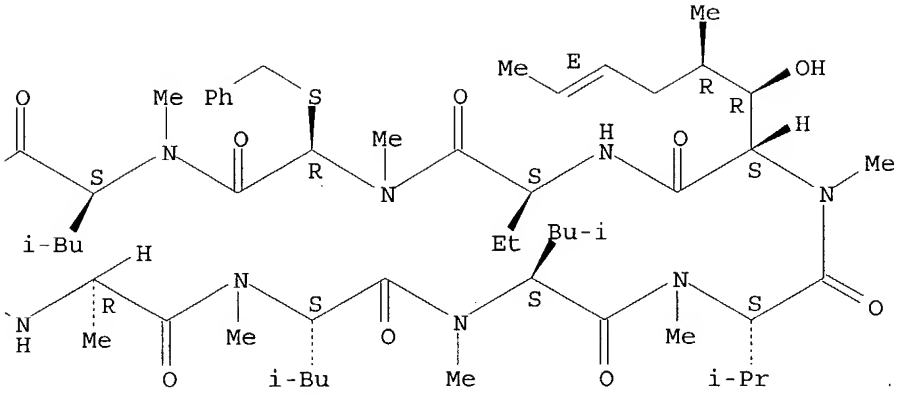
RELATED SEQUENCES AVAILABLE WITH SEQLINK

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



PAGE 1-B



1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

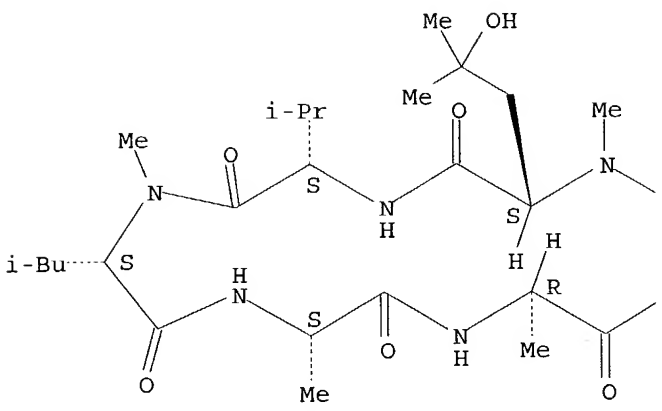
REFERENCE 1: 140:380253

L9 ANSWER 15 OF 74 REGISTRY COPYRIGHT 2004 ACS on STN
RN **676618-76-1** REGISTRY
CN Cyclosporin A, 6-[(3R,4S)-3-hydroxy-N-methyl-5-(methylthio)-L-leucine]-8-[(2R)-2-[[2-(dimethylamino)ethyl]thio]-N-methylglycine]-9-(4-hydroxy-N-methyl-L-leucine)- (9CI) (CA INDEX NAME)
FS PROTEIN SEQUENCE; STEREOSEARCH
MF C64 H118 N12 O13 S2
SR CA
LC STN Files: CA, CAPLUS
DT.CA CAplus document type: Journal
RL.NP Roles from non-patents: BIOL (Biological study); PREP (Preparation)

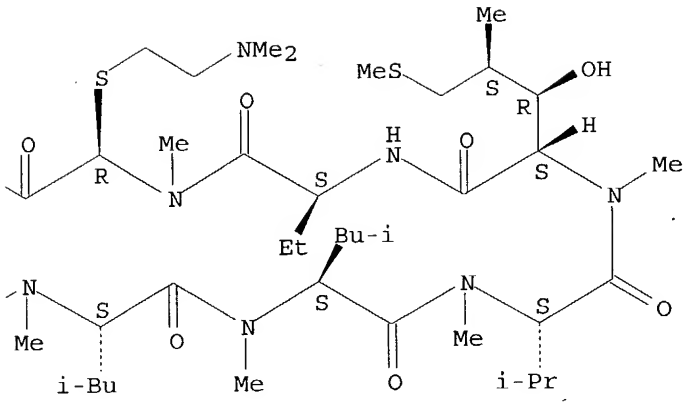
RELATED SEQUENCES AVAILABLE WITH SEQLINK

Absolute stereochemistry.

PAGE 1-A



PAGE 1-B



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

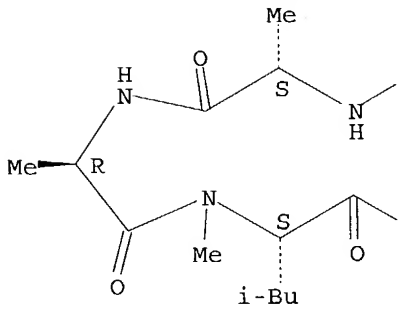
1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 140:304074

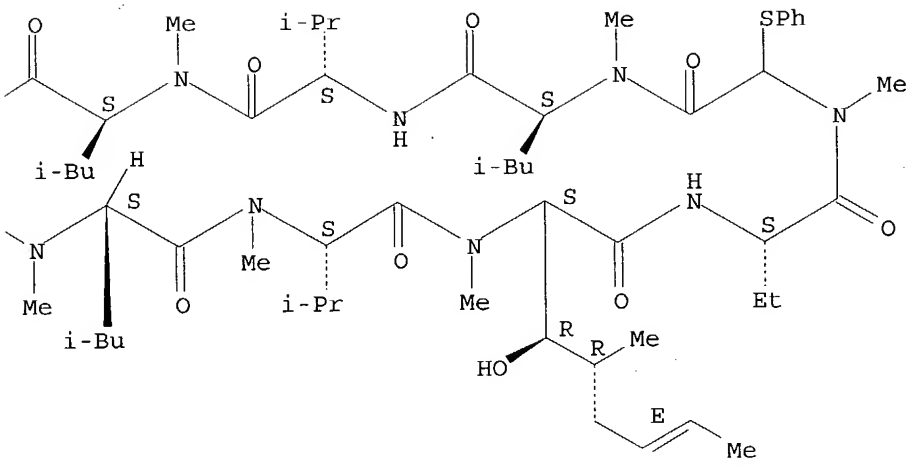
L9 ANSWER 20 OF 74 REGISTRY COPYRIGHT 2004 ACS on STN
RN **252760-03-5** REGISTRY
CN Cyclosporin A, 8-[N-methyl-2-(phenylthio)glycine]- (9CI) (CA INDEX NAME)
FS STEREOSEARCH .
MF C68 H115 N11 O12 S
SR CA
LC STN Files: CA, CAPLUS, USPATFULL
DT.CA CAplus document type: Patent
RL.P Roles from patents: BIOL (Biological study); PREP (Preparation); USES (Uses)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



PAGE 1-B



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

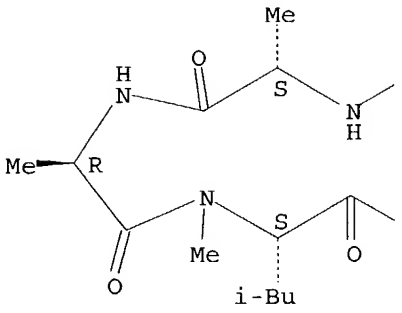
REFERENCE 1: 132:50254

L9 ANSWER 25 OF 74 REGISTRY COPYRIGHT 2004 ACS on STN
RN **252731-40-1** REGISTRY
CN Cyclosporin A, 8-[2-(acetyloxy)-N-methyl-2-(phenylthio)glycine]- (9CI) (CA INDEX NAME)
FS PROTEIN SEQUENCE; STEREOSEARCH
MF C70 H117 N11 O14 S
SR CA
LC STN Files: CA, CAPLUS, USPATFULL
DT.CA CAplus document type: Patent
RL.P Roles from patents: BIOL (Biological study); PREP (Preparation); USES (Uses)

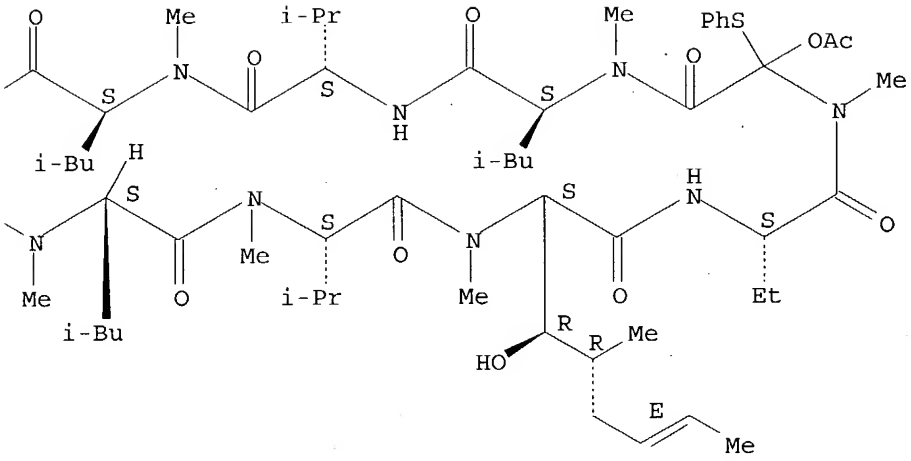
RELATED SEQUENCES AVAILABLE WITH SEQLINK

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



PAGE 1-B



1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

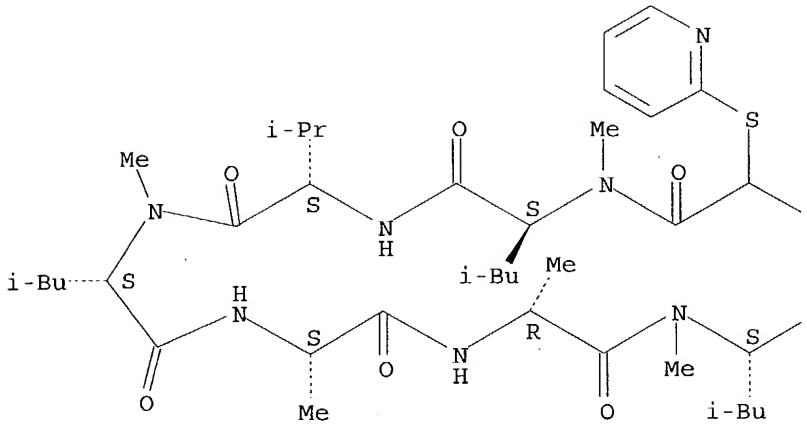
REFERENCE 1: 132:50254

L9 ANSWER 30 OF 74 REGISTRY COPYRIGHT 2004 ACS on STN
RN **252731-35-4** REGISTRY
CN Cyclosporin A, 7-L-norvaline-8-[N-methyl-2-(2-pyridinylthio)glycine]-(9CI) (CA INDEX NAME)
FS PROTEIN SEQUENCE; STEREOSEARCH
MF C68 H116 N12 O12 S
SR CA
LC STN Files: CA, CAPLUS, USPATFULL
DT.CA CAplus document type: Patent
RL.P Roles from patents: BIOL (Biological study); PREP (Preparation); USES (Uses)

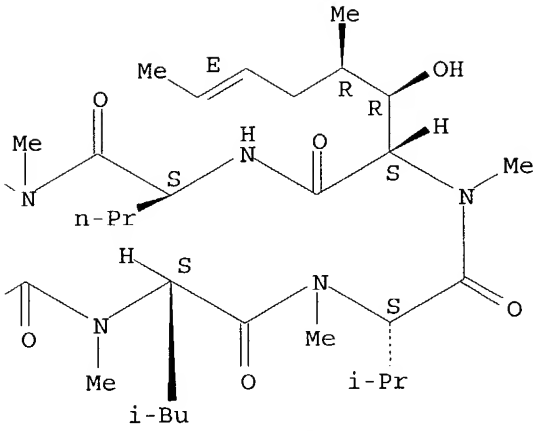
RELATED SEQUENCES AVAILABLE WITH SEQLINK

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



PAGE 1-B



1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

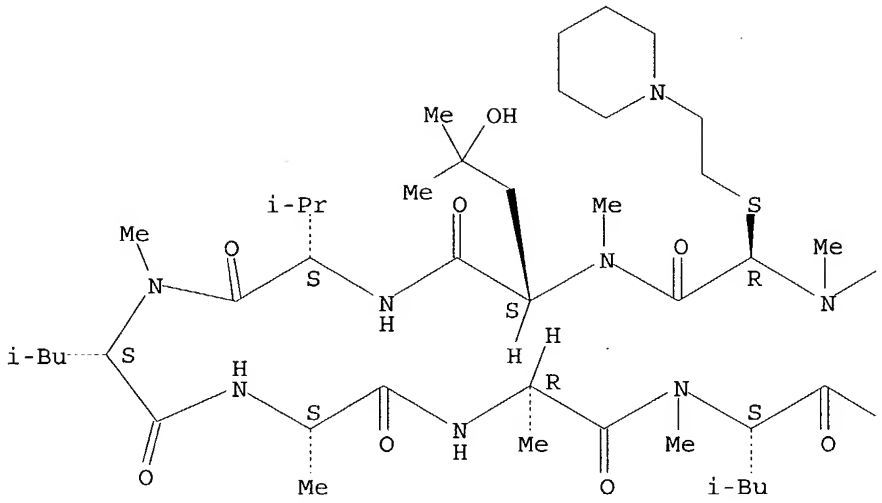
REFERENCE 1: 132:50254

L9 ANSWER 35 OF 74 REGISTRY COPYRIGHT 2004 ACS on STN
RN **227937-33-9** REGISTRY
CN Cyclosporin A, 8-[(2R)-N-methyl-2-[[2-(1-piperidinyl)ethyl]thio]glycine]-9-(4-hydroxy-N-methyl-L-leucine)- (9CI) (CA INDEX NAME)
FS PROTEIN SEQUENCE; STEREOSEARCH
DR 653586-07-3
MF C69 H124 N12 O13 S
SR CA
LC STN Files: CA, CAPLUS
DT.CA CAplus document type: Journal; Patent
RL.P Roles from patents: PREP (Preparation)
RL.NP Roles from non-patents: BIOL (Biological study); PREP (Preparation)

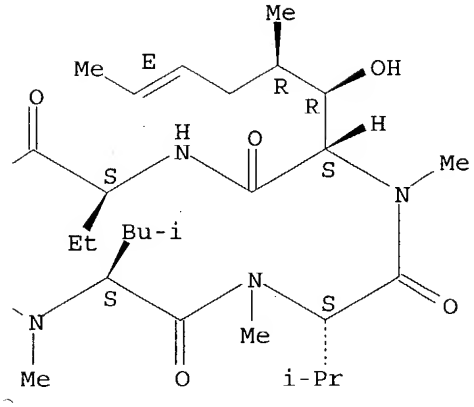
RELATED SEQUENCES AVAILABLE WITH SEQLINK

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



PAGE 1-B



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

2 REFERENCES IN FILE CA (1907 TO DATE)
2 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 140:146494

REFERENCE 2: 131:59141

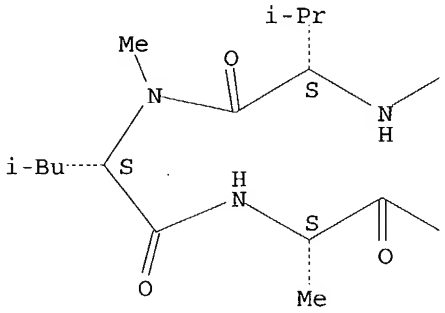
L9 ANSWER 40 OF 74 REGISTRY COPYRIGHT 2004 ACS on STN
RN **227937-26-0** REGISTRY
CN Cyclosporin A, 8-[(2R)-2-[[2-[[(1,1-dimethylethyl)dimethylsilyl]oxy]ethyl]

thio]-N-methylglycine]- (9CI) (CA INDEX NAME)
FS PROTEIN SEQUENCE; STEREOSEARCH
DR 653585-94-5
MF C70 H129 N11 O13 S Si
SR CA
LC STN Files: CA, CAPLUS
DT.CA CAplus document type: Journal; Patent
RL.P Roles from patents: PREP (Preparation); RACT (Reactant or reagent)
RL.NP Roles from non-patents: PREP (Preparation); RACT (Reactant or reagent)

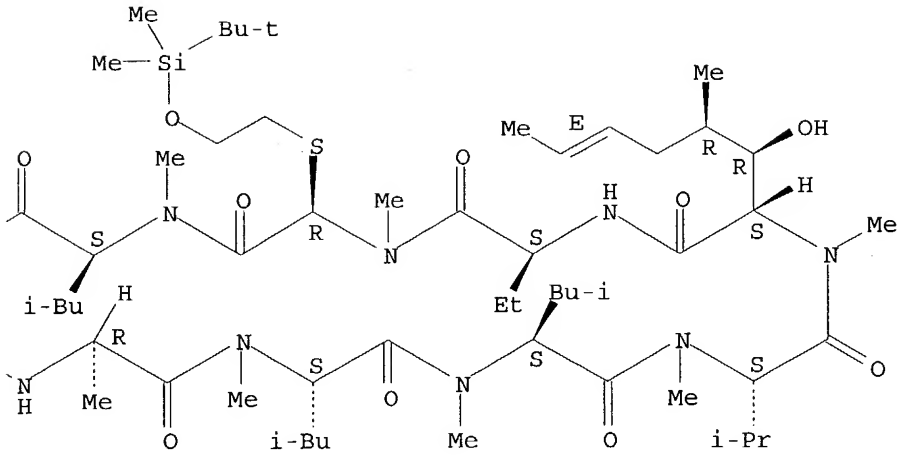
RELATED SEQUENCES AVAILABLE WITH SEQLINK

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



PAGE 1-B



2 REFERENCES IN FILE CA (1907 TO DATE)
2 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 140:146494

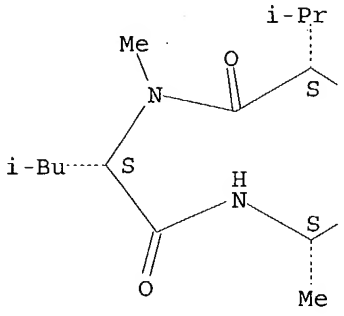
REFERENCE 2: 131:59141

L9 ANSWER 45 OF 74 REGISTRY COPYRIGHT 2004 ACS on STN
RN **215531-97-8** REGISTRY
CN Cyclosporin A, 6-[(2S,3R,4R,6E)-3-hydroxy-4-methyl-2-(methylamino)-8-(methylthio)-6-octenoic acid]-8-[(2R)-2-[[2-(diethylamino)ethyl]thio]-N-methylglycine]- (9CI) (CA INDEX NAME)
FS PROTEIN SEQUENCE; STEREOSEARCH
MF C69 H126 N12 O12 S2
SR CA
LC STN Files: CA, CAPLUS, USPATFULL
DT.CA CAplus document type: Patent
RL.P Roles from patents: BIOL (Biological study); PREP (Preparation); USES (Uses)

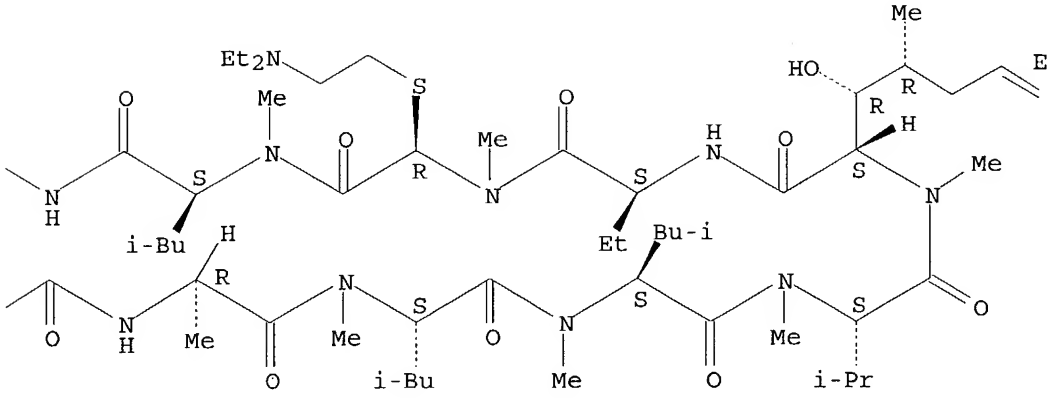
RELATED SEQUENCES AVAILABLE WITH SEQLINK

Absolute stereochemistry.
Double bond geometry as shown.

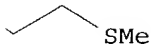
PAGE 1-A



PAGE 1-B



PAGE 1-C



1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

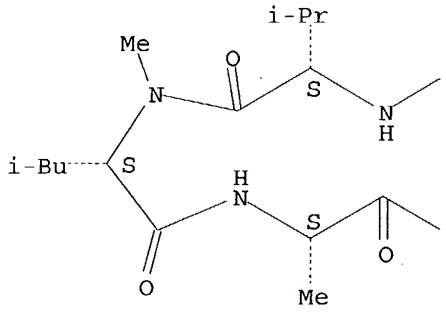
REFERENCE 1: 130:4088

L9 ANSWER 50 OF 74 REGISTRY COPYRIGHT 2004 ACS on STN
RN **210760-77-3** REGISTRY
CN Cyclosporin A, 8-[(2R)-2-[[2-(dimethylamino)ethyl]thio]-N-methylglycine]-(9CI) (CA INDEX NAME)
FS PROTEIN SEQUENCE; STEREOSEARCH
DR 653585-96-7, 674802-83-6
MF C66 H120 N12 O12 S
CI COM
SR CA
LC STN Files: CA, CAPLUS, USPATFULL
DT.CA CAplus document type: Journal; Patent
RL.P Roles from patents: BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
RL.NP Roles from non-patents: BIOL (Biological study); PREP (Preparation); USES (Uses)

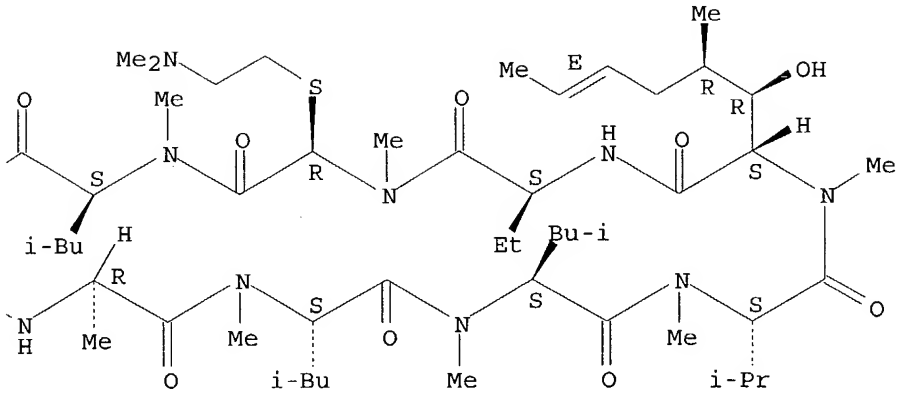
RELATED SEQUENCES AVAILABLE WITH SEQLINK

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



PAGE 1-B



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

4 REFERENCES IN FILE CA (1907 TO DATE)
4 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 140:263758

REFERENCE 2: 140:146494

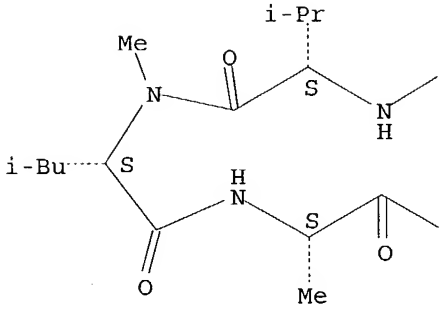
REFERENCE 3: 131:59141

REFERENCE 4: 129:149255

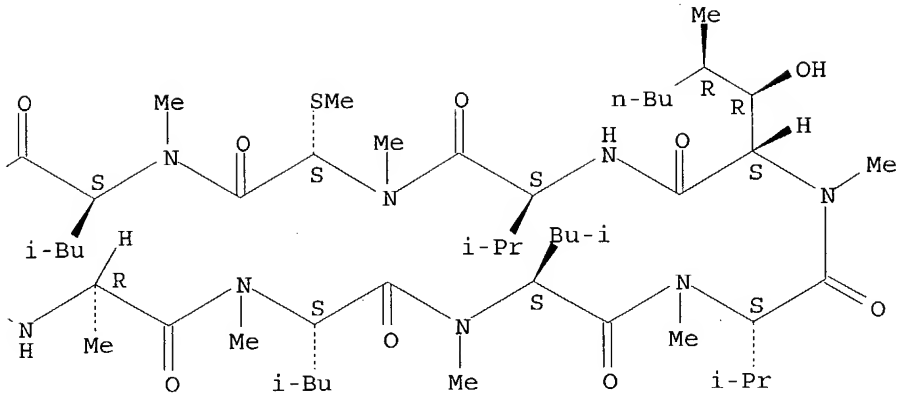
L9 ANSWER 55 OF 74 REGISTRY COPYRIGHT 2004 ACS on STN
RN **159992-08-2** REGISTRY
CN Cyclosporin A, 6-[(3R,4R)-3-hydroxy-N,4-dimethyl-L-2-aminooctanoic acid]-7-L-valine-8-[N-methyl-L-2-(methylthio)glycine]- (9CI) (CA INDEX NAME)
FS PROTEIN SEQUENCE; STEREOSEARCH
MF C64 H117 N11 O12 S
SR CA
LC STN Files: CA, CAPLUS
DT.CA CAplus document type: Journal
RL.NP Roles from non-patents: BIOL (Biological study)

Absolute stereochemistry.

PAGE 1-A



PAGE 1-B

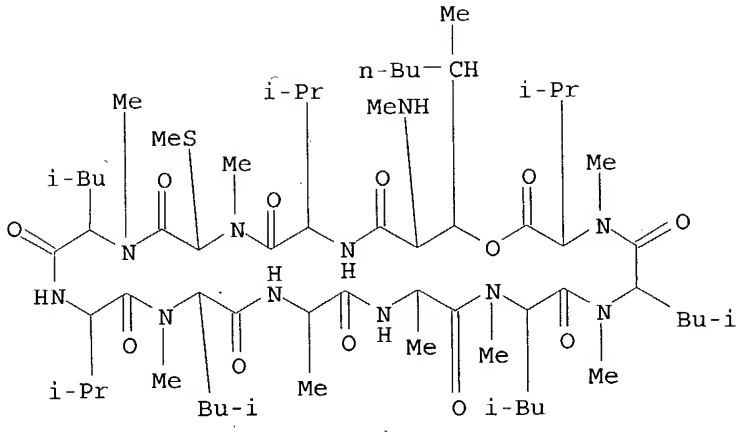


1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 122:45734

L9 ANSWER 60 OF 74 REGISTRY COPYRIGHT 2004 ACS on STN
RN **152546-97-9** REGISTRY
CN Isocyclosporin A, 1-[N-[3-hydroxy-4-methyl-2-(methylamino)-1-oxooctyl]-L-valine]-2-[N-methyl-(R)-2-(methylthio)glycine]-, monohydrochloride, [2S-(2R*,3S*,4S*)]- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN 1-Oxa-4,7,10,13,16,19,22,25,28,31-decaazacyclotetratriacontane, cyclic peptide deriv.
FS PROTEIN SEQUENCE
MF C64 H117 N11 O12 S . Cl H
SR CA
LC STN Files: CA, CAPLUS, TOXCENTER
DT.CA CAplus document type: Patent
RL.P Roles from patents: BIOL (Biological study); PREP (Preparation); USES (Uses)
CRN (152614-93-2)

RELATED SEQUENCES AVAILABLE WITH SEQLINK

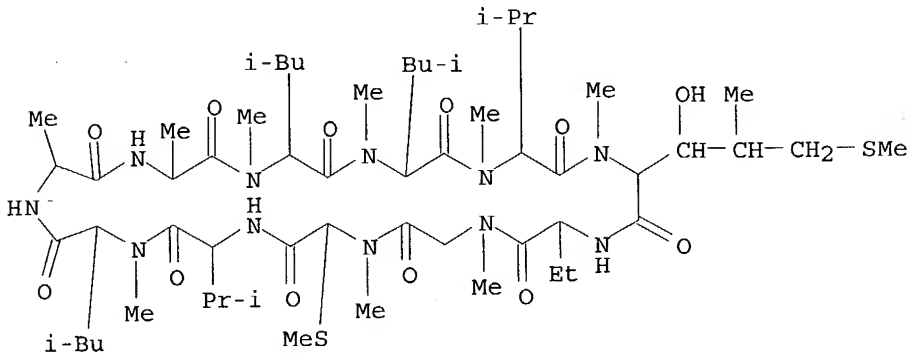


● HCl

1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 120:135131

L9 ANSWER 65 OF 74 REGISTRY COPYRIGHT 2004 ACS on STN
RN **122008-39-3** REGISTRY
CN Cyclosporin A, 6-[(3R,4R)-3-hydroxy-N-methyl-5-(methylthio)-L-leucine]-9-[N-methyl-L-2-(methylthio)glycine]- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN 1,4,7,10,13,16,19,22,25,28,31-Undecaazacyclotritriacontane, cyclic peptide deriv.
FS PROTEIN SEQUENCE
MF C57 H103 N11 O12 S2
SR CA
LC STN Files: CA, CAPLUS, USPATFULL
DT.CA CAplus document type: Patent
RL.P Roles from patents: BIOL (Biological study); PREP (Preparation); USES (Uses)



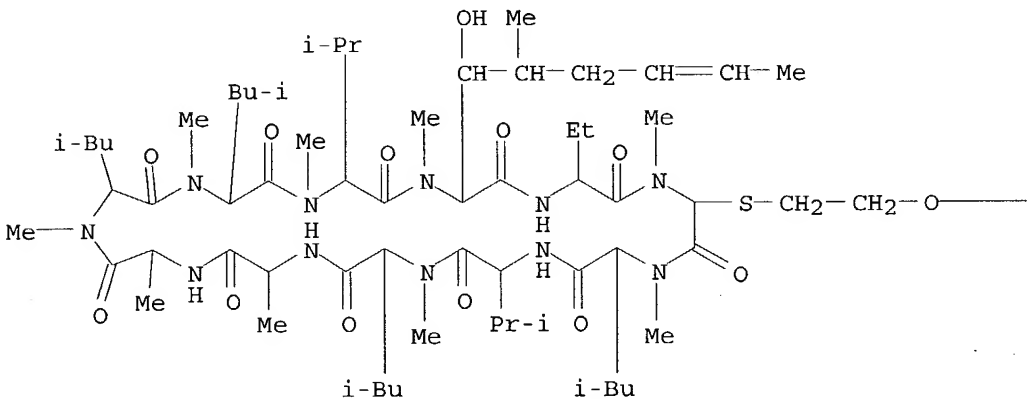
1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 111:97726

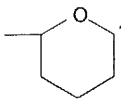
L9 ANSWER 70 OF 74 REGISTRY COPYRIGHT 2004 ACS on STN
RN **108466-64-4** REGISTRY
CN Cyclosporin A, 8-[N-methyl-D-2-[[2-[(tetrahydro-2H-pyran-2-yl)oxy]ethyl]thio]glycine]- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN 1,4,7,10,13,16,19,22,25,28,31-Undecaazacyclotritriacontane, cyclic peptide deriv.
FS PROTEIN SEQUENCE
MF C69 H123 N11 O14 S
SR CA
LC STN Files: CA, CAPLUS, USPATFULL
DT.CA CAplus document type: Patent
RL.P Roles from patents: PREP (Preparation)

RELATED SEQUENCES AVAILABLE WITH SEQLINK

PAGE 1-A



PAGE 1-B



1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 107:7610

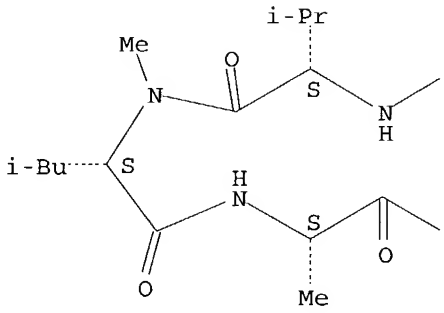
L9 ANSWER 74 OF 74 REGISTRY COPYRIGHT 2004 ACS on STN
RN **108466-60-0** REGISTRY
CN Cyclosporin D, 8-[(2R)-N-methyl-2-(methylthio)glycine]- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN 1,4,7,10,13,16,19,22,25,28,31-Undecaazacyclotritriacontane, cyclic peptide

deriv.
CN Cyclosporin A, 7-L-valine-8-[N-methyl-D-2-(methylthio)glycine]-
FS PROTEIN SEQUENCE; STEREOSEARCH
MF C64 H115 N11 O12 S
SR CA
LC STN Files: CA, CAPLUS, USPATFULL
DT.CA CAplus document type: Journal; Patent
RL.P Roles from patents: PREP (Preparation)
RL.NP Roles from non-patents: BIOL (Biological study); PROC (Process); PRP (Properties)

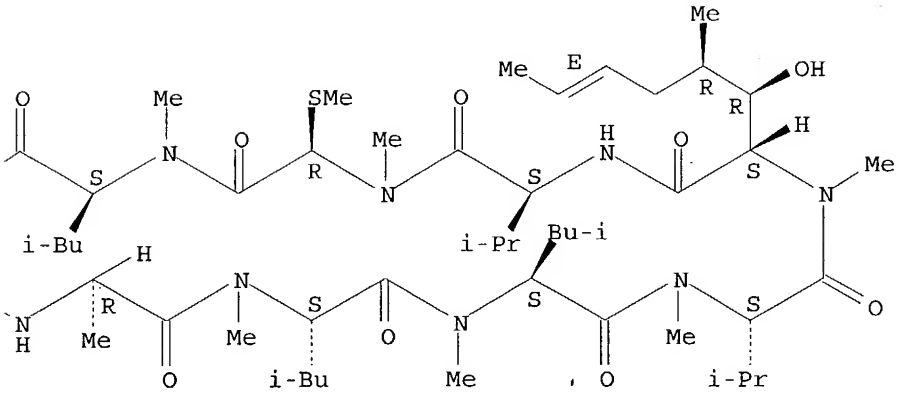
RELATED SEQUENCES AVAILABLE WITH SEQLINK

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



PAGE 1-B



2 REFERENCES IN FILE CA (1907 TO DATE)
2 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 130:90080

REFERENCE 2: 107:7610